Targeting of Nuclear Factor-κB and Proteasome by Dithiocarbamate Complexes with Metals

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Abstract: Dithiocarbamates and their complexes with transition metals have been used as common pesticides, vulcanizing or analytical agents for decades. These compounds are one of the most reported inhibitors of nuclear factor-κB (NF-κB) signaling cascade. Recently, it has been found that dithiocarbamates are very potent inhibitors of proteasome. NF-κB plays a central role in the immune system and is described as a major actor in many of human cancers mainly because of its protective effects against apoptosis. Molecular mechanisms involved in regulation and function of NF-κB pathway have been elucidated recently. In particular, pivotal zinc containing proteins that alter NF-κB signal transduction were recognized. Additionally, proteasome system was found to be a key player in NF-κB pathway and is an attractive target for anticancer drug development. Collectively, the capability of dithiocarbamates to inhibit NF-κB and proteasome makes these compounds promising anticancer agents. This review focuses on the biological activity of dithiocarbamate coordination compounds with regard to their possible molecular targets in NF-κB signaling and proteasome (JAMM domain proteins). Future research should aim to find the most suitable dithiocarbamate coordination compounds for treatment of cancer and other diseases.

Key Words: Disulfiram, Diethyldithiocarbamate (DDTC), Pyrrolidinedithiocarbamate (PDTC), Metal dithiocarbamates, NF-κB, Proteasome, JAMM.

THE PURPOSE OF THIS REVIEW

Chemistry of dithiocarbamates is more than one hundred years old, but it is still very vivacious and young due to many dithiocarbamate applications, that were revealed in past decades. In spite of myriads of dithiocarbamate compounds supplied by synthetic chemistry the demand for their use as inhibitors of nuclear factor-κB (NF-κB) has not been fulfilled yet. A reason for it might be a missing discussion between chemists and molecular biologists on this topic. Many basic questions remain largely open – from dithiocarbamate interactions with media components to their stability in cell. On the other hand it is still more evident in medicinal sciences that NF-κB pathway plays a pivotal role in many diseases such as cancer, AIDS or Alzheimer's dementia. Simultaneously current accomplishments in the field of NF-κB molecular biology encourage us to focus the attention on achieving specific targeting of proteins in the NF-κB signaling. One of the most important targets for antitumor therapy within these proteins seems to be ubiquitin-proteasome pathway (Nobel Prize in 2004). Therefore, it is exciting to read about recent findings concerning dithiocarbamate ability to inhibit proteasome through their metal complexes. The purpose of the present review, with respect of fact that the topic has never been reviewed, is to bridge various research-fields and to induce new inquiry (Fig. **1**) into this nascent development of new dithiocarbamate-based drugs.

INTRODUCTION

Dithiocarbamates are the reduced forms of thiuram disulfides (Fig. **2**) with strong complexing properties [1]. They exhibit very rich coordination chemistry with a large variety of transition metals (for reviews see [2-10]) and are used as vulcanizing [11-12] or analytical agents [13-15]. Thiuram disulfides (*thiram*), dithiocarbamate salts (*nabam*) or their complexes with iron (*ferbam*), manganese (*maneb*) and zinc (*ziram*, *zineb*, *propineb*, *metiram*) are well known as pesticides with an estimated annual global consumption of 25,000 – 35,000 metric tons [16].

These compounds are toxic for mammals [17-25] and can be involved in the etiology of Parkinson's disease [26-32]. Diverse functions of dithiocarbamates also include the use as antidotes against metal poisoning [33-37] and in cisplatin or carboplatin toxicity [38-41]. Iron dithiocarbamates are reactive towards nitric oxide and their nitrosyl complexes exhibit a characteristic EPR signal, so they have been used for the detection and analysis of biological NO produced endogenously from NO-synthases [42-52].

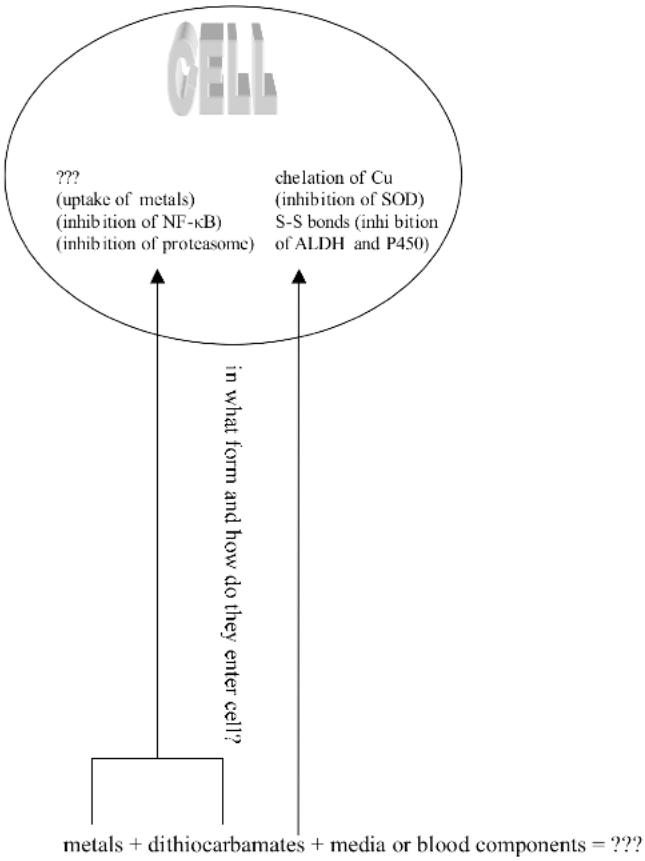

Fig. (1). Basic effects and unanswered questions of dithiocarbamate biological activity.

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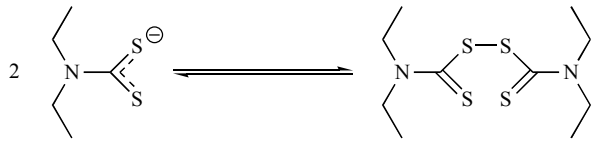
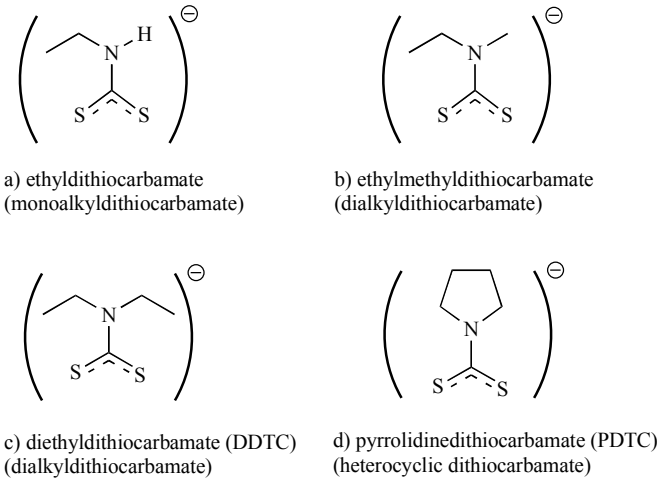


diethyldithiocarbamate (dithiocarbamate) — disulfiram (thiuram disulfide)

Fig. (2). Dithiocarbamates (reduced form) and thiuram disulfides (oxidized form).

Chemical properties of free dithiocarbamic acids and their salts have been known for decades [53-59]. These compounds are formed by the reaction between CS_2 and either ammonia or an amine in the presence of a base. If a diamine is used, a molecule with two dithiocarbamate groups can be obtained (e.g. ethylenebisdithiocarbamate). Since monoalkyldithiocarbamates (Fig. **3**) are more stable in acidic solutions, the half-life of diethyldithiocarbamate (DDTC) at pH 2 (0.3 seconds) shows the instability of dialkyldithiocarbamates at low pH. Their decomposition produces CS_2 and a dialkylamine. The stability of some dialkyldithiocarbamates was examined [60] at serum pH, resulting in the identification of novel stable dithiocarbamates, e.g. pyrrolidinedithiocarbamate (PDTC). The half-life for decomposition of PDTC is several orders of magnitude greater than that of DDTC (2.8×10^7 h vs. 12 h). Dithiocarbamates can be oxidized [58] to thiuram disulfides by iodine, bromine, ferricyanide and other oxidants. Oxidation of monoalkyldithiocarbamates possibly goes further to form the isothiocyanate and elemental sulfur. Complexes of dithiocarbamates (Fig. **4**) with metals are easily formed by adding a solution of the metal ion to a solution of ammonium or alkali metal dithiocarbamate. These compounds are sparingly soluble in water but are soluble in non-polar organic solvents, so they are widely believed to be lipophilic enough to pass through the cell membrane (see below).



a) ethyldithiocarbamate (monoalkyldithiocarbamate)

b) ethylmethyldithiocarbamate (dialkyldithiocarbamate)

c) diethyldithiocarbamate (DDTC) (dialkyldithiocarbamate)

d) pyrrolidinedithiocarbamate (PDTC) (heterocyclic dithiocarbamate)

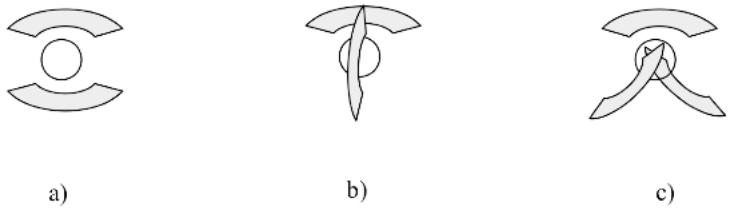
Fig. (3). Dithiocarbamates are divided into four groups: a) monoalkyldithiocarbamates, dialkyldithiocarbamates (b) unsymmetric or c) symmetric) and d) heterocyclic dithiocarbamates.

GENERAL BIOLOGICAL ACTIVITY OF DITHIOCARBAMATES

Disulfiram was used as a scabiescide and, subsequently, as a vermicide in the 1930s because it is capable of chelating copper, an essential component of the respiratory chain of lower animal forms [61]. It has been used under the trade name Antabuse in the treatment of chronic alcoholism since 1940s [62-69] and has been in development for management of cocaine abuse [70-73] (it increases brain dopamine concentrations by inhibition of dopamine catabolising enzymes). Disulfiram, as used in the aversion therapy of recovering alcoholics, is described to react specifically with human liver aldehyde dehydrogenase (ALDH) E1 with a loss of catalytic activity and without incorporation (DDTC is formed and the number of enzyme thiol groups decreases during this process) [74]. However, incorporation could be detected within the first few minutes when ALDH was inhibited by disulfiram [75]. It seems that the ALDH inhibition by disulfiram is caused by the formation of an intramolecular disulfide bond between the active site thiol and the thiol of another cysteine residue [76-77]. Nevertheless, there are other possible mechanisms of disulfiram inhibitory action on ALDH *via* its metabolites [78-84]. Disulfiram is believed to exert its effect after P-450-dependent metabolism [85-86]. The findings of [87-88] suggest that *N*-dealkylation may be an important pathway in disulfiram oxidative metabolism and that the inhibition of ALDH occurred by carbamoylation caused by disulfiram metabolites.

Under acidic conditions (see above), the decomposition of dithiocarbamates to their corresponding amines and CS_2 is favored [89]. CS_2 mediates protein cross-linking and is proposed to be an important molecule behind dithiocarbamate-induced toxicity [90]. The free thiol groups of dithiocarbamates can react with thiol groups of other molecules, so they have been reported to inhibit enzymes by covalent interaction with free protein thiols [1, 91] as well as to oxidize glutathione through a glutathione peroxidase-like activity [92-93]. They can also interfere with cellular detoxication mechanisms as they are described to suppress hepatic microsomal drug metabolism [94] and to inhibit glutathione *S*-transferases [95] or to deplete intracellular glutathione in a non-superoxide dismutase-dependent manner [96-97].

DDTC is a putative immunomodulator known as ditiocarb (or imuthiol) [98-101] and proposed to enhance immune responses in the treatment of AIDS [102-107]. DDTC acts as a potent chelator to remove copper from superoxide dismutase (SOD) [108-109]. This reaction apparently leads to a cooperative binding of two DDTC to copper ion (complex of two DDTC with Cu(II) is well described in [110]) with consequent removal of the metal from the protein. Copper depleted SOD can be easily and rapidly prepared by this way [111]. DDTC inhibits also endogenous SOD *in vivo*, this inhibition is not reversed by dialysis, but it is reversed by incubation with



a) b) c)

Fig. (4). Dithiocarbamate ligands (coordinated through their two sulfurs) in a) square planar (metal : ligand = 1 : 2), b) tetrahedral (metal : ligand = 1 : 2), c) octahedral (metal : ligand = 1 : 3) complexes.

$CuSO_4$ after dialysis [112]. Thus, DDTC in low concentration may protect cells from the deleterious effects by hydroxyl radicals generated in the presence of SOD and H_2O_2 [113]. Together with DDTC-mediated inhibition of ALDH and SOD it is widely used as P450 inhibitor [114]. Although DDTC has been postulated to inactivate P450 by binding covalently to the apoprotein [115], the most known effect of DDTC on CYP2E1 is metabolism-dependent [116]. DDTC is not at all inhibitory toward CYP2E1 at a low concentration but was significantly inhibitory toward CYP2A6 and CYP2B6 activities [116-119]. Disulfiram, hovewer, inhibits CYP2E1 and not CYP2A6 *in vivo* [120].

In fact, no wonder dithiocarbamates may both inhibit and induce apoptosis because of their pleiotropic action on cells [121]. In short-term incubations, they inhibit apoptosis induced by a variety of agents. It has been argued that this indicates the role of ROS (reactive oxygen species) in apoptosis [122-123]. Conversely, others suggest that inhibition of apoptosis *via* dithiocarbamates may relate to oxidation of critical thiols rather than general scavenging of oxygen radicals [124]. Thus, disulfiram inhibits caspase-3, caspase-1 (they show different sensitivity to disulfiram *in vitro*), and most likely other family members [125]. In addition, these authors speculate on a role of metabolic degradation of disulfiram in disulfiram-induced apoptosis. Although thiuram disulfides themselves are antiapoptotic by virtue of their interaction with caspases, with time this effect is lost as the inhibitor is metabolized. Dithiocarbamate induce apoptosis *via* an intracellular uptake of copper [126]. They are probably converted by copper-catalyzed reaction to thiuram disulfides, which are potent oxidants of glutathione [127]. The authors propose to describe the dithiocarbamates as radical-scavening compounds (they remove one-electron oxidants) with pro-oxidant activity (glutathione oxidation).

Furthermore, several studies have reported that dithiocarbamates can promote cellular uptake of copper and zinc [128-130] and induce copper-mediated neurological disorders [131-136]. PDTC complex with Cu(II) decreases mitochondrial membrane potential, depletes glutathione and differentially activates c-Jun N-terminal kinases (JNK), extracellular signal-regulated kinases (ERK), p38 and caspase-3 in the cultured rat cortical astrocytes [137]. From other findings, it appears that zinc is an integral element in PDTC-mediated bovine cerebral endothelial cell death [138] and that PDTC-mediated accumulation of intracellular zinc may affect cell viability by modulating several signaling pathways in embryonic hippocampal progenitor cells [139]. These results put together, it is not surprising that dithiocarbamate-induced apoptosis depends on cell type, density and the presence of copper and zinc in medium [140-141] or that, moreover, it is biphasic [142]. Finally it must be noted that dithiocarbamates apparently trigger the release of cytochrome *c* into the cytosol [143-144].

Despite these studies, disulfiram continues to be used clinically [145]. There are only few adverse effects associated with long term treatment [146]. Hepatotoxicity is the most common and serious cause for concern during the treatment with disulfiram. Reports from Denmark indicate that over a 22-year period fatalities associated with disulfiram induced hepatotoxicity were 1 per 30 000 patients [147]. This liver damage is generally reversible if disulfiram is stopped prior to clinical manifestation [148]. The pharmacokinetics of disulfiram has also been extensively studied. There is more than 80% bioavailability after an oral dose and the elimination of disulfiram and its metabolites is a slow process. About 20% of the drug remains in the body for 1-2 weeks post-ingestion [149].

Disulfiram inhibits P-glycoprotein-mediated multidrug resistence (MDR), a frustrating problem in the clinic to formulate effective chemotherapy against cancer. This occurs by inhibiting the maturation (glycosylation) of the P-glycoprotein transporter [150]. Moreover, disulfiram inhibits the ATP-dependent molecular pumps that extrude anticancer agents from the cells [151] and is a potent modulator of multidrug transporter Cdr1p of *Candida albicans* [152]; hence it may be useful for anticancer as well as antifungal therapy [153].

INHIBITORS OF NF-κB PATHWAY

Nuclear factor-κB (NF-κB) regulates the expression of cytokines, growth factors, and effector enzymes in response to ligation many receptors involved not only in immunity [154]. It orchestrates the expression of genes outside of the immune system and, hence, it influences multiple aspects of normal and disease physiology [155-176]. NF-κB plays a pivotal role in regulating expression of a number of proinflammatory genes. It makes this nuclear factor an attractive target for therapeutic intervention [177-190]. There is, furthermore, the relationship between HIV replication and NF-κB action [191-195]. Activation of NF-κB can contribute to the oncogenic state in several ways: by driving proliferation, by enhancing cell survival, or by promoting angiogenesis or metastasis [196-209]. From neurological point of view, pharmacological and genetic manipulations of NF-κB pathway were developed. This may be valuable in the treatment of various disorders such as Alzheimer's disease or schizophrenia [210-217].

NF-κB family comprises five members: p65 (RelA), RelB, c-Rel, p50/p105 (NF-κB1), and p52/p100 (NF-κB2); they exist in unstimulated cells as homo- or heterodimers. The signaling pathway (Fig. **5**) by which cytokines (e.g. tumor necrosis factor-α, TNF-α), lipopolysaccharides (LPS) or other agents induce formation of p50:p65 heterodimer and trigger its nuclear translocation is known as the canonical or classical NF-κB pathway [218-219]. In resting cells, p50:p65 is bound to the inhibitor-κB (I-κB) protein and this complex is retained in cytoplasm [220-223]. Cell stimulation triggers signal transduction that ultimately results in the activation of a specific I-κB kinase (IKK) [224]. IKK is a complex composed of three subunits: IKKα (IKK1), IKKβ (IKK2), and IKKγ (NF-κB essential modulator, NEMO) – and plays a crucial role in the NF-κB activation [225-229]. Phosphorylation of I-κB by IKK tags it for ubiquitination by a specific ubiquitin ligase belonging to SCF (Skp-1/Cul/F box) family [230]. Upon ubiquitination, the I-κB protein is rapidly degraded by the proteasome. NF-κB is concomitantly liberated from multiprotein complex and heterodimer p50:p65 goes to the nucleus where it binds to DNA and triggers transcription [231-232]. Neveretheless, degradation of I-κB and nuclear translocation of heterodimer are not sufficient to promote a maximal NF-κB transcriptional response. Rather, the NF-κB complex must undergo additional post-translational modifications [233].

Dithiocarbamates are known as inhibitors of the canonical NF-κB pathway since 1992 [234]. Using cell culture experiments, DDTC, disulfiram and PDTC are shown there to be potent blockers of NF-κB activation. The efforts of the authors concentrated on PDTC that does not change the pH of the culture medium (*cf* [58, 60]). Even at micromolar concentrations, PDTC was effective in the inhibition of NF-κB. Because of this, PDTC did not affect the level of the cytoplasmic complex of the heterodimer with I-κB and could not interfere with its DNA binding or nuclear uptake, it most likely blocked the release of I-κB and its degradation (*cf* [235]).

In fact, pretreatment of rats with PDTC inhibited the LPS-induced I-κB degradation, reduced neutrophil accumulation in lungs, heart, and liver and attenuated increase in microvascular endothelial permeability induced by LPS in these organs [236]. However, the efficacious concentration of PDTC is narrow: the minimal concentration of PDTC required for inhibition of NF-κB lies between 25 and 50 mg/kg, whereas at the PDTC concentration of 200 mg/kg animals showed toxic effects manifested as hypersalivation, excitability, and neuromuscular irritability (*cf* [131-139]). Furthermore, PDTC has to be administred before the challenge, because it was ineffective in inhibiting NF-κB when given concurrently with LPS. These findings have been strongly supported by other studies in which PDTC has been shown to down-regulate the expression of NF-κB controlled genes *in vivo* [237-

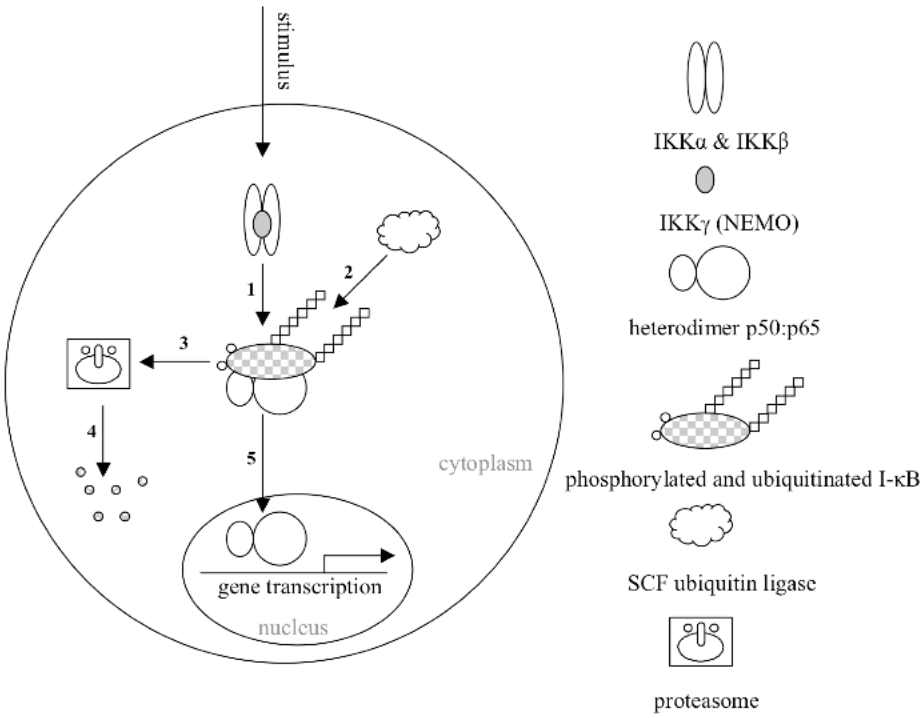


Fig. (5). Canonical NF-κB pathway. IKK complex phosphorylates I-κB (1) to induce its rapid ubiquitination (2) and degradation by proteasome (3, 4). Associated NF-κB heterodimer is thereby released to translocate into the nucleus (5), where it modulates gene transcription.

249]. Moreover, PDTC can attenuate an acute injury even if it fails to inhibit NF-κB [250-251].

There are hundreds of papers dealing with the use of dithiocarbamates as NF-κB inhibitors *in vitro*. Since most of these papers are not focused on the inhibition mechanism they have not been included into this review (with the exception of the following six citations). PDTC was proposed as a tool to explore the expression of genes involved in the inflammatory response [252-254]. However, PDTC-induced inhibition of NF-κB is not a universal phenomenon [255] and like dithiocarbamate toxicity (see above) it is biphasic [234, 256].

It has been proposed that NF-κB is responsive to oxidative stress [257-259] and hence that it is inhibited by antioxidants, for instance dithiocarbamates [260-261]. In contrast, NF-κB activation seems to be rather more complex and well orchestrated intracellular event, which may not depend on oxygen radicals [262-265]. Thus, as this pathway becomes more defined, and more levels of regulation are described, many antioxidants believed to inhibit NF-κB because of their effects on ROS will possibly be shown to act through other targets. Indeed, a number of studies have shown interactions between NF-κB and transition metals or their compounds [266]. It was revealed that Zn^{2+} ($ZnSO_4$), Au^{3+} ($AuCl_3$) and Cu^{2+} ($CuSO_4$), which have similar properties in binding to thiol and imidazole groups in proteins, are potent inhibitors of IKK complex [267]. Some results indicate that Cu^{2+} inhibits the release of NF-κB by the blockade of a signal leading to the phosphorylation of I-κB [268] and that PDTC inhibits the TNF-α-dependent activation of NF-κB by increasing intracellular level of copper [269]. However, copper in the form of copper-histidine complex triggers activation of NF-κB in the liver and lung of rats [270]. Hence, it seems that this is not the metal ion alone but rather a coordination compound with its chemical properties that is important for altering NF-κB. For example, zinc is described to be either essential for [271] or to exert an inhibitory effect on NF-κB binding to DNA [272]. Furthermore, zinc is probably the serum factor that is required for PDTC-induced inhibition of NF-κB activity [273]. It is noteworthy that thiol compounds in contrast to non-thiol ones, when co-administered with PDTC, rather abolish the action of this dithiocarbamate. This is probably due to the reaction of Zn^{2+} with the thiol moiety [274]. Consistently, various thiols modulate dithiocarbamate effects on NF-κB pathway [275-278].

PROTEASOME INHIBITORS IN ANTITUMOR THERAPY

Proteasome [279], an energy-dependent protease found in all three domains of life (*Bacteria*, *Archaea*, and *Eucarya*), is a key regulator of many other cellular events including NF-κB signaling. This system is essential for the protein turnover and maintanence of protein quality by degrading misfolded and denatured proteins [280]. Proteasome is important for cell development and division, cell metabolism and DNA repair [281-283]. Furthermore, proteasome controls the distribution, abundance, and activity of the transcriptional machinery [284-286] and has a functional link to translation initiation [287]. Proteasome has nonproteolytic roles in the cell, including those involved in nucleotide excision repair [288], recruitment of histone acetyltransferases to target promoters [289], transcription elongation [290-291], and cell cycle control [292]. Therefore, the possibility of targeting proteasome was met with great skepticism at the very beginning. However, with the demonstration that proteasome inhibitors were well tolerated and had activity in models of human malignancies *in vivo*, the proteasome inhibitor bortezomib was introduced for the treatment of relapsed multiple myeloma with clinical evidence demonstrating efficacy and safety [293].

Known proteasome inhibitors comprise five classes: a) peptide aldehydes, b) peptide vinyl sulfones, c) peptide boronates, d) peptide epoxyketones, and e) β-lactones, based on the pharmacophore that reacts with a threonine residue in the active site of the proteasome [294]. Although inhibition of proteasome has been largely investigated as a promising approach for anticancer therapy [295-296], bortezomib is currently the only proteasome inhibitor approved for the clinical treatment of human cancer [297]. There are many proposed mechanisms to explain the antitumor activity of

proteasome inhibitors [298], but more studies are required to confirm benefits of this new approach in oncology.

Recently, it has been shown, that complexes $Cu(DDTC)_2$ and $Zn(DDTC)_2$ (for crystal structures see [110, 299]) are selectively toxic to melanomas over normal cells and may provide a means of selectively targeting melanoma *in vivo* [300-301]. In comparison with diverse metals (including Zn), the ability of DDTC complexes with metals to exert cytotoxicity in breast carcinoma cells differs, and only $Cu(DDTC)_2$ is an effective antitumor agent [302]. PDTC decreases the viability and proliferation of renal carcinoma cell lines, but not normal cells [303]. More recently, pharmacological profiling of disulfiram encourages its clinical studies as anticancer agent [304]. The use of the disulfiram in the clinic is further supported by a case report where this compound in combination with zinc gluconate induced clinical remission in a patient with metastatic ocular melanoma [305].

The essential question is: How is NF-κB pathway blocked by Cu^{2+} and Zn^{2+} dithiocarbamate complexes? The answer explains anticancer effect of dithiocarbamates. Research of antiviral activity of PDTC revealed strong influence of this dithiocarbamate with aqueous Cu^{2+} or Zn^{2+} solutions on polyprotein processing and ubiquitin-proteasome pathway of host cell [306-307]. Indeed, incubation of the 20S proteasome with Zn^{2+} drastically inhibits its activities with no effect on oxidative status of proteasome [308-309]. It has been shown that PDTC-induced inhibition of proteasome depends on Zn^{2+} ions [310]. Both mentioned papers [308-310] also propose Cu^{2+} ions as potent inhibitors of proteasome. In further studies, dithiocarbamate complexes with copper were reported to inhibit proteasome [311-313] and to be promising tools for anticancer therapy analogous to those with platinum, palladium and gold [314-316]. Of course, metal ions are not free of coordinated ligands (e.g. water molecule) in aqueous solution and the chemical nature of the ligand determines their capability of inhibiting the proteasome [317-318]. This, from molecular point of view, encourages us to ask what type of coordination sphere and which interaction with proteins is responsible for metal-dependent proteasome inhibition.

POSSIBLE TARGET: JAMM DOMAIN PROTEINS

The whole scene of targeting the ubiquitin-proteasome system [297] is of course too complex to deal with adequately in this review, but here are some speculations. Interaction of coordination spheres of two metal ions can lead to their rearrangement and substantial change in their chemical properties. Inasmuch as NF-κB pathway depends on multiple proteins with zinc finger (e.g. NEMO [227]) or RING (really interesting new gene) finger (e.g. ubiquitin ligases [319]) motifs, one could speculate about direct interaction of dithiocarbamate complexes with a coordinated Zn^{2+} ion. Although dithiocarbamates were reported as ubiquitin ligases inhibitors [320-321], it is appropriate to interpret this effect and proteasome inhibition together.

The function of both proteasome and SCF ligase depends on JAMM (JAB1/MPN/Mov34 metalloenzyme) domain proteins that belong to a novel family of metallopeptidases [322]. The arrangement of zinc ligands in JAMM resembles that one present in thermolysin and serves to hydrolyze ubiquitin conjugates in a manner similar to this enzyme [323]. Activity of JAMM enzymes, which are essential for SCF ligase and proteasome, can be blocked by metal chelators (*o*-phenanthroline) or metal ions (zinc acetate, nickel chloride) [324-325]. This is tentatively the molecular basis of metal dithiocarbamate-induced proteasome inhibition. In addition, and contrary to JAMM, matrix metalloproteinases, which exhibit different zinc binding environment [326], are more sensitive to ligand and in this case zinc abrogates disulfiram-induced metalloproteinase inhibition [327].

JAMM plays an important role in the regulation of activating protein-1 known as AP-1 (c-Jun:c-Fos heterodimer) and p53, which both are affected by dithiocarbamates. PDTC promotes a rapid upregulation of c-*fos* and c-*jun* mRNA levels and they induce heme oxygenase 1 and manganous superoxide dismutase genes through the activation of AP-1 [328-330]. Interestingly, proteasome inhibitors trigger induction of heme oxygenase 1 gene due to p38 and AP-1 cascade [331] and proteasome (with intact JAMM motif only) can selectively rescue c-Jun from the degradation [332]. Proteasome inhibitors also induce a prominent increase of p53 levels and p53-dependent form of apoptosis in cancer cells [333]. Indeed, dithiocarbamates increase the level of p53 and promote p53 nuclear uptake through the accumulation of copper in cells [334]. There is the JAMM motif again that seems to be important in p53 cytoplasmatic translocation and subsequent degradation [335]. Future studies hopefully show which JAMM proteins play role in AP-1 and p53 signaling and the mechanisms of their interaction with dithiocarbamate complexes.

FUTURE DIRECTIONS

Currently, there are many novel inhibitors of NF-κB pathway and NF-κB-DNA binding under development [336-341]. Dithiocarbamates, perhaps for their pleiotropic cellular effects, fall outside attention. Up to date there are no reports on structure-activity relationship for dithiocarbamate derivatives (although there are some exceptions, such as [342-343]) and their complexes with diverse metals. One could suggest that metal complexes, which do not possess reactive thiol groups, will be well focused proteasome inhibitors with negligable adverse effects, but the research of synthetic dithiocarbamate complexes as such inhibitors is only at the beginning. Most recently, a synthetic dithiocarbamate complex (with Au^{3+}) has been shown for the first time to inhibit proteasome [344]. The design of new dithiocarbamate complexes as NF-κB and proteasome inhibitors is therefore a promising aim for future extensive research and cooperation of inorganic chemists with molecular biologists and physicians.

In addition, several basic questions remain unanswered. What is the role of metal binding in various dithiocarbamate biological effects? What is the molecular target and mechanism of their proteasome inhibition? There are further questions of chemical reactivity of dithiocarbamate ligands with transition metals in culture media and of stability of formed complexes in biological systems. Surprisingly, it is still not clear how they enter cell. Our preliminary results show that the polarity of these compounds is comparable with that of methanol. Hence, it does not seem likely that they freely cross the cell membrane lipid bilayers as small non-polar molecules do. We tested two synthetic zinc dithiocarbamates on HeLa cells with interesting results: $Zn(BDTC)_2$ (BDTC = dibenzyldithiocarbamate) inhibited TNF-α-induced NF-κB nuclear translocation but Zn(DDTC) elicited nulear translocation (unpublished results). Further research should elucidate the exact nature of this phenomenon with a focus on molecular interactions between dithiocarbamate coordination compounds and NF-κB pathway.

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ABBREVIATIONS

NF-κB = Nuclear factor-κB

JAMM = JAB1/MPN/Mov34 metalloenzyme

JAB1 = Jun activating binding protein

MPN = Mpr1p Pad1p N-terminal domain metalloenzyme motif

DDTC = Diethyldithiocarbamate

PDTC = Pyrrolidinedithiocarbamate

ALDH = Aldehyde dehydrogenase

SOD = Superoxide dismutase
ROS = Reactive oxygen species
JNK = c-Jun N-terminal kinases
ERK = Extracellular signal-regulated kinases
TNF-α = Tumor necrosis factor-α
I-κB = Inhibitor-κB
IKK = I-κB kinase
NEMO = NF-κB essential modulator
SCF = Skp-1/Cul/F box
RING = Really interesting new gene
AP-1 = Activating protein-1
BDTC = Dibenzyldithiocarbamate

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