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Groundbreaking gold(III) anticancer agents

Among the large number of new molecules reported as innovative anticancer agents characterized by both significant antineoplastic activity and minimal systemic toxicity, gold(III)-dithiocarbamato complexes stand out from the other chemotherapeutics. The potential of these compounds, deliberately designed to combine the 'bullet' character of the metal center with the stabilizing effect of the sulfur chelating ligands, has been increasingly apparent during the past few years. In this regard, efforts to meet the need of a marked antitumor activity together with the decrease of severe side-effects, led to the development of some tailored molecules designed to improve the therapeutic effectiveness of the clinically established anticancer drugs.

To date, several complexes stabilized with *S*-donor ligands have been synthesized, thus preventing the possible subsequent reaction with sulfur-containing biomolecules once administered. In fact, it is well-known that sulfur-containing proteins and enzymes may interact with heavy metals, and these side-reactions are responsible for the toxicity induced by the platinum drugs, in particular nephrotoxicity, and also for the onset of tumor cell resistance to metal chemotherapeutic agents [1]. To achieve this goal, some dithiocarbamato derivatives of amino acids have been selected as ligands. Actually, dithiocarbamates are able to bind strongly to soft metals, thus possibly preventing further interaction with sulfur-containing biomolecules and protecting against cisplatin-induced nephrotoxicity in several animal models [2]. Moreover, the gold(III) metal center was chosen, because of its square-planar tetracoordinated geometry, resembling platinum(II), and its possible reduction, in physiological medium, to gold(I) species, whose anticancer activity had been previously reported already.

General formulas of the investigated gold(III) complexes are shown in Fig. 1.

Screening for *in vitro* cytotoxicity of gold(III)-dithiocarbamato compounds on a panel of human tumor cell lines, highlighted that all the studied complexes exhibited relevant cytotoxic activity toward all the tested cell lines. They appeared to be much more potent than cisplatin even at nanomolar concentration, with IC_{50} values about one- to four-fold lower than that of the reference drug [3]. They also exerted a potent antiproliferative and apoptotic effect against acute myelogenous leukemia (AML) cell lines representing different French–American–British (FAB) subtypes and in the Philadelphia positive (Ph+) cell line (K562) carrying the BCR–ABL fusion gene product, with IC_{50} values about ten-fold lower than cisplatin [4]. Gold(III) compounds are also active against cell lines intrinsically resistant to cisplatin, such as colon (LoVo) and non-small cells lung (A549) adenocarcinoma lines, suggesting a possible lack of cross-resistance with cisplatin [5,6]. To assess this hypothesis, three human tumor cell lines and their clones were selected for resistance to cisplatin: 2008/C13* (human ovarian carcinoma), A431/A431-R (human squamous cervix carcinoma) and U2OS/U2OS-R (human osteosarcoma). All the tested gold(III) complexes were cytotoxic against the cisplatin-resistant cell lines, with activity levels comparable to those induced on the parent sensitive lines, ruling out the occurrence of cross-resistance phenomena [5,6]. Gold(III) compounds caused immediate damage to the cells, slightly affecting cell cycle, thus suggesting a different mechanism of action compared to platinum-based drugs [3,6].

Preliminary evaluation of *in vivo* antitumor activity has been carried out on ascitic and solid Ehrlich tumor-bearing mice, and gold(III) complexes proved noticeably more active than cisplatin in both slackening tumor growth and increasing the life span of treated animals [7]. As for systemic toxicity, gold(III) compounds showed to be less toxic than cisplatin, with LD_{50} values of about 35 mg kg^{-1} and 10 mg kg^{-1}, respectively. Furthermore, *in vitro* and *in vivo* nephrotoxicity studies have confirmed that these compounds induce very low renal toxicity compared to cisplatin [7]. All together, these data support the hypothesis of a different mechanism of action [6].

The proteasome has been recently identified as a major *in vitro* and *in vivo* target for these gold(III)-dithiocarbamato derivatives [8,9], potently reducing proliferation in different breast cancer cell lines, including premalignant MCF10K.cl2, malignant MCF10dcis.com, estrogen receptor α-positive MCF7 and estrogen receptor α-negative MDA-MB-231 cells. The tested gold(III) complexes inhibit the proteasomal chymotrypsin-like activity in highly metastatic and invasive MDA-MB-231 whole cell extract in a concentration-dependent way. This evidence is particularly important because it has been reported that inhibition of proteasomal chymotrypsin-like but not trypsin-like activity is associated with growth arrest and/or apoptosis induction in cancer cells [10,11]. Moreover, inhibition of proteasome activity and accumulation of p27 were also detected on xenograft tumors: treatment of MDA-MB-231 tumor-bearing nude mice resulted in a significant inhibition (about 50%) of tumor growth, as a consequence of the proteasomal inhibition and the massive induction of apoptosis. During the daily treatment at 1.0 mg kg^{-1} for 29 days, no toxicity was observed, and mice did not display any sign of weight loss, decreased activity, or anorexia [8].

These exciting results prompted further investigation aimed at studying their mechanism

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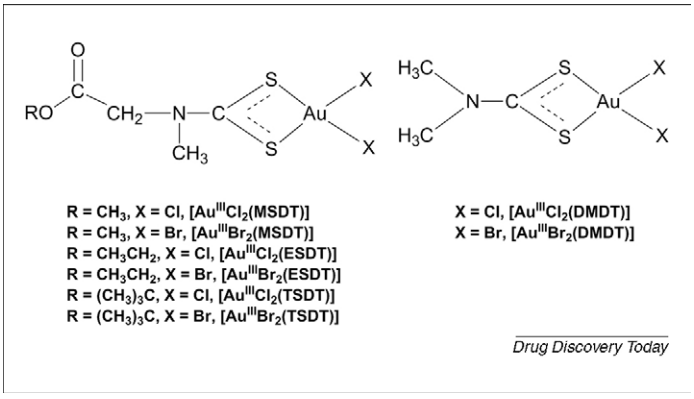

FIGURE 1

Selected Au(III)-dithiocarbamato derivatives: X = Cl, Br; DMDT = *N*,*N*-dimethyldithiocarbamate ($(CH_3)_2NCSS^-$); MSDT = methylsarcosinedithiocarbamate ($CH_3O(O)CCH_2N(CH_3)CSS^-$); ESDT = ethylsarcosinedithiocarbamate ($CH_3CH_2O(O)CCH_2N(CH_3)CSS^-$); TSDT = *t*-butylsarcosinedithiocarbamate ($(CH_3)_3CO(O)CCH_2N(CH_3)CSS^-$).

of action in-depth. As a natural continuation, the effect of gold(III)-dithiocarbamato compounds on mitochondrial functions was examined. The compounds trigger cell death by activating both apoptotic and non-apoptotic pathways. They are able to alter some mitochondrial functions, such as membrane potential and permeability conditions, stimulate reactive oxygen species (ROS) generation, strongly inhibit the activity of the selenoenzyme thioredoxinreductase (TrxR), and increase ERK-1/2 phosphorylation [11]. On the basis of such results, it was proposed that gold(III) compounds might exert their activity by inhibiting TrxR activity [12] and stimulating production of ROS, which then oxidize and inactivate the proteasome [13] and/or other molecules involved in the ubiquitin/proteasome pathway [14].

All together, these results confirm the enormous potential of this class of gold(III) complexes as anticancer agents, thus making them worthy of further preclinical investigations aimed at their recognition as suitable candidates for clinical trials.

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