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Copper homeostasis as target of both consolidated and innovative strategies of anti-tumor therapy

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ABSTRACT

Background: Copper was reported to be involved in the onset and progression of cancer. Proteins in charge of copper uptake and distribution, as well as cuproenzymes, are altered in cancer. More recently, proteins involved in signaling cascades, regulating cell proliferation, and anti-apoptotic protein factors were found to interact with copper. Therefore, therapeutic strategies using copper complexing molecules have been proposed for cancer therapy and used in clinical trials.

Objectives: This review will focus on novel findings about the involvement of copper and cupro-proteins in cancer dissemination process, epithelium to mesenchymal transition and vascularization. Particularly, implication of well-established (e.g. lysil oxidase) or newly identified copper-binding proteins (e.g. MEMO1), as well as their interplay, will be discussed. Moreover, we will describe recently synthesized copper complexes, including plant-derived ones, and their efficacy in contrasting cancer development.

Conclusions: The research on the involvement of copper in cancer is still an open field. Further investigation is required to unveil the mechanisms involved in copper delivery to the novel copper-binding proteins, which may identify other possible gene and protein targets for cancer therapy.

1. Biology of copper

Copper is an essential transition metal required for the biochemistry of all living organisms. It plays a key role as a catalytic cofactor in oxidation-reduction (redox) reactions; it donates and accepts electrons, shifting between its oxidized (CuII) and reduced (CuI) forms. In biological systems, copper is bound to proteins, by complexation with cysteines, histidines and methionines, and to low molecular compounds [1,2]. In humans, enzymes requiring copper are involved in several pathways of metabolism. Cu/Zn superoxide dismutase 1 and 3 (SOD1 and SOD3) act in free radicals' detoxification while cytochrome c oxidase in ATP production in mitochondria. Both ceruloplasmin and haephestin are ferroxidases involved in iron homeostasis. Moreover, lysyl oxidase (LOX) participates to collagen fibrils formation, while tyrosinase in the synthesis of melanin [3]. Copper ions are also fundamental for enzymes involved in the physiology of the nervous system, like dopamine β monooxygenase (DBM, catecholamines synthesis) or peptidylglycine α-amidating monooxygenase (PAM, neuropeptide synthesis) [3]. Moreover, more recently, it has been shown that also proteins involved in cell signaling cascades or cell differentiation and death are modulated by copper, expanding the role of copper in other processes of cell physiology and pathology.

Due to its redox properties, unbound copper is highly reactive and it may catalyze the Haber-Weiss reaction between the partially reduced oxygen species superoxide anion ($O_2^{-\cdot}$) and hydrogen peroxide (H_2O_2) producing the highly aggressive hydroxyl radical (OH·) [4]. These

Abbreviations: APP, amyloid precursor protein; ATOX1, antioxidant-protein 1; ATP7A/ATP7B, Cu-transporting P-type ATPases; CCS, Cu chaperone for superoxide dismutase 1; CDDP, cisplatin; COX, cytochrome c oxidase; CQ, clioquinol; CTR1 (*SLC31A1*), high affinity copper transporter; Cu, copper; DBM, dopamine β monooxygenase; DMT1, divalent metal trasporter 1; DSF, disulfiram; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; GPER, G-protein estrogen receptor; Grx1, glutaredoxin 1; HCC, hepatocellular carcinoma; HRE, hypoxia responsive elements; IL, interleukin; IRS, insulin receptor substrate; L-OHP, oxaliplatin; LMP, lysosomal membrane permeabilization; LOX, lysyl oxidase; MBDs, metal binding domains; MDR, multidrug resistance; PAM, peptidylglycine α-amidating monooxygenase; ROS, reactive oxygen species; SOD1/3, superoxide dismutase 1 and 3; TF3, theaflavin-3,30-digallate; TGFβ, transforming growth factor β; TTM, tetrathiomolybdate; UPP, ubiquitin-proteasome pathway; VEGF, vascular endothelial growth factor

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reactive oxygen species (ROS) could damage lipids, proteins, nucleic acids, and other biomolecules, leading to cell death [5]. Thus, to prevent undesired side reactions, copper is bound to committed proteins for its escort into cells and deliver to the cuproenzymes [6,7] and to small molecules rich in cysteines for its detoxification (e.g., glutathione and metallothioneins) and virtually no free copper is present in the cells [8,9].

The recommended daily intake of copper in healthy adults is 0.9 mg/day. Copper is absorbed in the small intestine and is then transported in blood, primarily by serum albumin, to the liver and to other organs for subsequent delivery to apo-enzymes [3]. The cellular uptake of reduced copper (included the dietary pool) relies on the high affinity membrane copper transporter CTR1, encoded by the *SLC31A1* gene, the deletion of which is lethal in embryos [10]. Human CTR1 is a trimeric protein, forming a pore in the membrane. Each monomer shows an extracellular N-terminal domain, comprising two motives rich in histidine and two rich in methionine, involved in Cu(II) binding and reduction. Three transmembrane domains are also present: TMD1 and TMD2, both rich in methionine, which interact with copper, and TMD3, which is essential for CTR1 oligomerization. Cytoplasmic C-terminal end occludes the pore and, following copper binding, undergoes conformational changes, allowing the intracellular delivery of the metal [11,12]. When copper plasma level is elevated, CTR1 is internalized and degraded, preventing that excess and potentially noxious copper enters the cell; on the contrary, in case of copper deficiency, CTR1 membrane levels increase [13]. *SLC31A1* gene transcription is under the control of Sp1 zinc-finger transcription factor. The zinc finger domain of Sp1 functions as a copper sensor, regulating CTR1 expression in response to variations in copper concentration. Moreover, CTR1 levels and function seems to be also modulated by the cytosolic CTR2, a protein homologous to CTR1, which was demonstrated to stimulate CTR1 degradation [14].

Once in the cell, copper is delivered to its enzyme targets following three different routes, sustained by specific metallochaperones, showing the conserved copper-binding motif (MTCXXC) [15]. In the cytosol, the Copper Chaperone for Superoxide dismutase (CCS) binds copper and delivers it to SOD1 [15]. CCS is a reliable sensor of intracellular copper levels: it is degraded by proteasomal activity upon copper-sufficiency and increases upon copper depletion [16]. In the secretory route, the copper chaperone ATOX1 (Antioxidant-protein 1, also known as HAH1) transfers copper to P-type ATPases ATP7A and ATP7B, localized on the membrane of the *trans* Golgi network. ATP7A and B are membrane protein pumps characterized by 8 transmembrane domains (TMDs), which include multiple Cu-binding sites mainly located at TM6, TM7, and TM8 [17,18]. Moreover, ATP7A and ATP7B show six metal-binding domains at the N-terminus (N-MBD), each with a CXXC motif. It has been suggested that protein folding of the CXXC metal binding motifs of ATPases, similar to that present in ATOX1, may promote rapid intermolecular metal transfer from ATOX1 to ATPases through electrostatic, hydrogen bonding, and hydrophobic interactions [19]. One or the other of the pumps donate copper in the lumen to enzymes to extracellular fate, like CP or LOX, during their synthesis [20]. The pumps ATP7A and B have a tissue–specific expression: ATP7A in enterocytes (allowing dietary copper entrance in the body) and other tissues (including the nervous system), while ATP7B is present mainly in the liver thus allowing copper excretion with bile. In response to high intracellular copper levels, ATP7A and ATP7B moves within endocytic vesicles, towards basolateral or apical membranes, respectively [21]. The vesicles fuse with the plasma membrane, transferring excess copper out of the cell [22]. ATP7B N-terminus can interact with a cytosolic protein, COMMD1 (Copper Metabolism MURR1 Domain-containing 1), which might regulate pump stability and thus biliary excretion of copper. COMMD1 is an intriguing pleiotropic protein; it is involved in many cell pathways, particularly in the modulation of transcription factors like NF-κB and HIF-1α (hypoxia inducible factor 1α) [23]. Indeed, deletion of COMMD1 gene results in embryonic lethality [24].

Mitochondrial copper pool, essential for synthesis and stability of cytochrome c oxidase (COX), the terminal enzyme of the respiratory chain, is provided by the cytosolic copper chaperone COX17 [25] and other proteins (including SCO1, SCO2 and COX11), to be eventually incorporated into subunits I and II of COX [25]. COX is embedded in the inner mitochondrial membrane where it catalyzes the transfer of electrons from reduced cytochrome c to molecular oxygen and contributes to the formation of proton gradient. In mammals, it is composed of 13 structural subunits. The catalytic core of the enzyme is constituted by three mitochondrially-encoded subunits (COX I–III). Highly conserved domains within subunits I and II contain two heme moieties (heme a and a3) and three copper ions (Cu_A, binuclear, and Cu_B) essential to its catalytic activity. The assembly of a fully active enzyme proceeds in a modular fashion through three distinct intermediates. The COX chaperones SCO1 and SCO2 share a high degree of sequence similarity, particularly in their C-terminal region that protrudes into the intermembrane space (IMS) and contains a conserved CXXC motif deputed to the binding of copper. Although it has been widely demonstrated that COX17 donates copper to SCO proteins and another chaperone, COX11, is required for the biogenesis of the Cu_A and Cu_B sites, respectively, how these chaperones are themselves metallated within the IMS remains unclear [26]. More recently, it has been also reported that SCO1 regulates CTR1-dependent copper import highlighting the role of mitochondria in cellular copper homeostasis [27].

The importance of copper homeostasis in humans is demonstrated by the severe clinical consequences of two genetic disorders, Menkes' and Wilson's diseases, which show systemic copper deficiency or overload, respectively. Menkes' disease is an X-linked recessive disorder fatal to infant boys, due to mutation to the gene coding for ATP7A, thus impeding copper trespassing of enterocytes and resulting in whole body copper deficiency. The disease is characterized by several symptoms, like a failure to thrive, hypotonia, kinky hair (*pili torti*), deterioration of the nervous system, and severe intellectual disability. Wilson's disease is an autosomal recessive disorder, caused by mutations to the gene coding for the ATP7B pump, and thus characterized by accumulation of copper mainly in the liver and several other organs (e.g., brain, kidney) with resulting redox copper toxicity (e.g. liver cirrhosis) [28–30]. The differential phenotype of these diseases derives from the tissue-specific expression of ATP7A and B: ATP7A is mainly expressed in enterocytes, while ATP7B is present mainly in the liver. Mutation of COMMD1 is also associated to a genetic disease: in dogs, the deletion of exon 2 of the COMMD1 gene causes copper accumulation and toxicosis [31].

The dysregulation of copper homeostasis results not only in genetic disorders such as the above cited ones, but also in neurodegenerative diseases, i.e. Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis and prion-mediated encephalopathies [32,33]. Furthermore, several studies suggest a strong correlation between altered copper levels and dysregulation of proteins involved in copper homeostasis and the onset and progression of cancer [34].

This review will focus on novel findings about the involvement of copper and cupro-proteins in onset, angiogenesis and dissemination of cancer. Particularly, implication of well-established (e.g. lysil oxidase, LOX) or newly identified copper-binding proteins (e.g. MEMO1), as well as their interplay, will be considered as novel potential targets for therapy. The mechanisms underlying copper-modulated anticancer drugs effects will be discussed. Moreover, we will illustrate consolidated or newly synthesized copper-binding molecules, as well as some plant-derived ones, and their efficacy in contrasting cancer development by targeting different cellular pathways.

2. Copper-Cancer connection

2.1. Copper and cell-proliferation

The first evidence of copper metabolism derangement in cancer dates back to 1965 [35], when De Jorge et al. demonstrated that in

brain cancer copper level was up to 11 times higher than in parental brain cells. Later on, Schwartz [36] pointed out the potential roles of trace elements, including copper, as carcinogens and their possible use as diagnostic/prognostic markers. Since then, experimental data showed an increased copper levels in several tumor cell types, despite normal levels of other trace elements, such as zinc, selenium or iron [37,38]. Copper imbalance in cancer is confirmed by increased copper levels in stage I multiple myeloma [39], in acute lymphoblastic leukemia [40], lung cancer [41], reticulum cell sarcoma, bronchogenic and laryngeal squamous cell carcinomas, cervical, breast, stomach [42].

In order to understand the origin of copper imbalance in cancer, recently, the human copper proteome was studied in 18 different tumor types, using RNA transcript data available in the TCGA database. Copper transporters CTR1, ATOX1, ATP7B, COX17 were up-regulated in breast cancer. This suggests that there is an increased copper flow *via* CTR1, followed by loading onto copper-dependent enzymes *via* the ATOX1-ATP7B path, and increased delivery of copper to mitochondria via COX17 and SCO2. In prostate cancer, the involvement of copper dysregulation seems controversial. Indeed, it has been demonstrated that only a subset of prostate cancer patients from the Victorian Cancer Biobank (Melbourne, Australia) harbors elevated intratumoral copper levels, irrespective of their disease stage, prostate specific antigen (PSA) expression level and serum copper concentration [43]. On the contrary, both prostate cancer patients [44] and *in vitro* cultured prostate primary (PrEC), hyperplasic (BPH-1) and carcinoma (PC3, Du145 and LNCaP) cell lines were characterized by 2–6 fold higher copper levels and by a higher basal expression levels of CTR1, ATP7A and ATP7B [45,46].

Other studies strongly suggest a relationship between copper-binding proteins/chaperones and cell proliferation. It was demonstrated that ATOX1 acts as a copper-dependent transcription factor. Once bound to copper, it migrates to the nucleus where it binds to a *cis* sequence in the promotor of the gene coding for the cyclin D1, thus promoting its transcription and prompting cell replication [47].

Later on, the discovery that MEK1 is a copper-binding protein led to the hypothesis that copper is involved in the RAS-RAF-MEK-ERK signaling cascade, required for cancer development (Fig. 1). Upon ligand binding to the receptor tyrosine kinases, the RAF family members (HRAS, KRAS and NRAS) are activated and, in turn, induce the dimerization of the RAF family members (BRAF and CRAF) leading to the activation of the MER/ERK signaling cascade [48]. BRAF is among the most frequently mutated kinases in tumors and the V600E mutation results in the constitutive activation of the MEK1 and MEK2 kinases. Then, the phosphorylation and activation of the ERK1 and ERK2 kinases occurs, thus chronically stimulating the mitogen-activated protein kinase (MAPK) pathway, eventually leading to cancer [48]. By *in vitro* experiments, Turski et al. [49] demonstrated a dose-dependent stimulation by copper of MEK1 kinase activity. Copper-binding may stimulate the MEK1-ERK interaction, promoting ERK phosphorylation. Equilibrium binding studies with MEK1 clarify thermodynamics of the binding reaction: MEK1 can bind 2 atoms of Cu(II) with high affinity and specificity. However, the authors did not address the kinetic of the binding and did not identify copper ligands within MEK1. To date, it is still obscure how MEK1 is loaded with copper and the mechanisms underlying the requirement of copper for solid MEK1/2 kinase activity have not been explained. However, it has been shown that the decreased influx, bioavailability and binding of copper to MEK1 decrease MEK1 kinase activity and also the oncogenic BRAF-driven tumorigenesis [50]. In addition, the decrease of intracellular copper accumulation, due to the reduction of CTR1 protein levels or loss of CTR1 function, results in impaired insulin/FGF-stimulated activation of RAS/MAPK signaling, affecting ERK phosphorylation [49,50]. Overall, these data strongly suggest that increased copper levels promote cell proliferation and tumorigenesis.

XIAP (the cytoplasmic X-linked Inhibitor of Apoptosis Protein), which shows E3 ubiquitin ligase activity, hinders caspases, thus inhibiting apoptotic cell death; its expression is increased in several

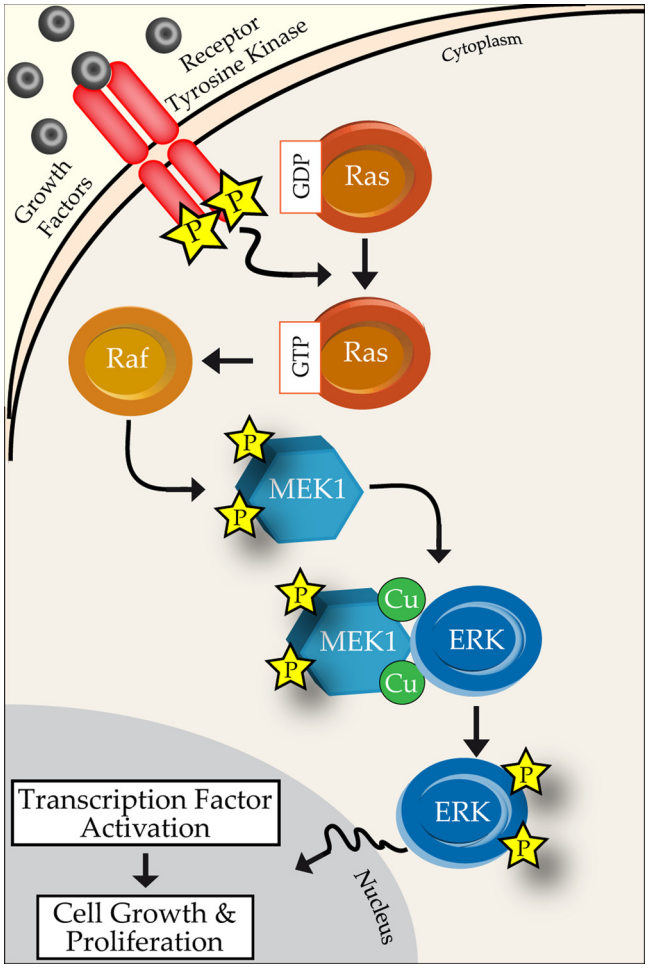

Fig. 1. Schematic proposal for the copper modulation of the RAS/RAF/MEK1 cascade. The binding of growth factors (i.e. VEGF, EGF) resulted in the phospho-activation of the Receptors Tyrosine Kinase (RTKs), which, in turn activates the RAS signaling cascade. Upon phosphorylation, the direct binding of two copper atoms to MEK1 induces conformational change in MEK1, promoting its productive interaction with ERK and thus subsequent ERK phosphorylation.

cancers [51,52]. It was found that XIAP can coordinate copper, donated by CCS [53], through binding to the cysteine-rich BIR domain and the RING finger domains [54]. XIAP seems to play a role in copper homeostasis, because it also targets CCS. CCS ubiquitination does not resulted in its degradation but increased its ability to deliver copper to its physiologic target, SOD1 [53] (Fig. 2). Furthermore, XIAP regulates copper balance by interaction and subsequent ubiquitination and degradation of COMMD1, one of the protein involved in copper export, thus leading to the increase of copper levels [55].

However, XIAP not only regulate copper homeostasis but, in turn, it is regulated by the intracellular copper levels. Indeed, when copper levels are increased, as in Wilson's disease, copper triggers reversible conformational changes in XIAP, thus promoting XIAP degradation [56] (Fig. 2). This evidence unveils an unpredicted connection between copper and apoptosis *via* XIAP.

2.2. Copper in cancer progression

Processes like creation of pre-metastatic niches, escape of immune defense, and angiogenesis, sustain cancer progression and metastasis. Indeed, many recent reports (reviewed in [57]) demonstrate that copper and copper-binding proteins are involved in vascular remodeling, immunity, inflammation and metastatic diffusion of tumors.

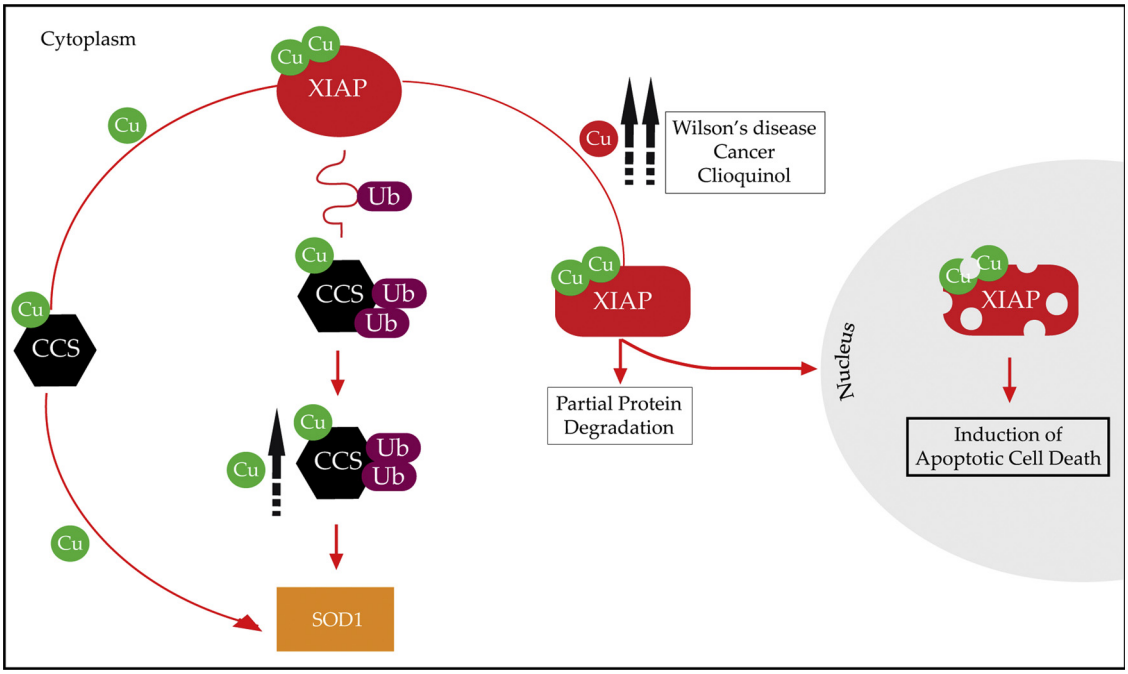

Fig. 2. Copper involvement in XIAP function. The copper chaperone for SOD 1 (CCS) delivers copper to the XIAP cysteines rich BIR domain and RING finger domains. In presence of increased pathological copper levels (Wilson's disease, cancer and after CQ treatment) copper triggers reversible conformational changes in XIAP, inducing protein degradation. On the other hand, CCS itself is target of the E3 ubiquitin ligase activity of XIAP. Interestingly, CCS ubiquitinaton results in an increased ability of the copper chaperone to bind copper and deliver it to its physiologic target, SOD1.

Early adaptation to microenvironmental factors like hypoxia is an early feature of the growing tumor, and in this process HIF-1 plays a pivotal role [58]. HIF-1 is composed by a constitutively expressed β-subunit and an oxygen-labile α-subunit. In normoxia, HIF-1α is destabilized by prolyl hydroxylation, an enzymatic activity requiring O_2, resulting in proteasomal degradation. Under limiting O_2 conditions (hypoxia), the ubiquitination of HIF-1α is prevented. As a result, HIF-1α accumulates, dimerizes with HIF-1β, and activates transcription of target genes involved in cancer progression or apoptosis by interaction with the hypoxia responsive elements (HREs). It has been demonstrated that copper and CCS are required to activate HIF-1 through the regulation of binding to HRE and the formation of the HIF-1 transcriptional complex [59]. Copper inhibits prolyl hydroxylase thus stabilizing HIF-1α [60]. Furthermore, in hepatic and breast cancer cells copper is able to induce the expression of HIF-1α through the activation of the EGFR/ERK/c-fos transduction pathway [61]. Moreover, HIF-1-mediated gene expression is regulated by interaction with COMMD1, which disrupts HIF-1 dimerization [31].

Copper involvement in the building of the extracellular matrix (ECM) may proceed through the activity of the copper-dependent enzyme LOX [62], which catalyzes the cross-linking of collagen and elastin in the ECM. HIF-1α induces LOX expression and, in turn, enzymatic activity of LOX promotes the synthesis of HIF-1α protein, following the activation of the PI3K/Akt pathway. Therefore, a synergistic action and regulation of both proteins results in promoting tumor progression [63,64].

One of the main processes involved in tumor growing is angiogenesis, a crucial step for the formation of new blood vessels from pre-existing blood vessels [65]. Angiogenesis involves the migration, proliferation and differentiation of endothelial cells to form new blood vessels. It is under control of angiogenic stimulating factors (e.g., angiogenin, vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF] and transforming growth factor β [TGFβ]) and cytokines (interleukin [IL]-1, -6 and -8) as well as through inhibitors (e.g., angiostatin and endostatin). Copper seems to be involved throughout the angiogenic signaling cascade affecting the proteins involved in the cascade both directly (by binding) and indirectly (regulating their expression/release) [66]. For example, copper increases the transcription of several angiogenic genes (e.g. ceruloplasmin and VEGF) by modulating the activation of HIF-1. Ceruloplasmin, as well as its protein fragments, binds copper ions and induces the formation of new blood vessels [60]. Furthermore, copper ions increase the production of the inducer of vascular dilation nitric oxide (NO) through the activation of the endothelial Nitric Oxide Synthetase (eNOS) [66]. In human umbilical vein endothelial cells (HUVEC), it was found that the conditioned medium from breast cancer cells treated with copper promoted cell migration and tube formation through HIF-1α and the G-protein estrogen receptor (GPER) signaling [61].

Copper transporters and chaperones are also involved in angiogenesis. Indeed, silencing the CTR1 expression in HUVEC cell lines treated with copper, inhibited the angiogenesis as well as reduced VEGF expression [67]. Again, in HUVEC cells where copper depletion was obtained by exposure to three peptides derived from the copper-binding regions of CTR1, inhibition of proliferation, migration, and tube formation was observed [68]. In addition, ATOX1 may act as an angiogenesis modulator: when binding copper it may act as a transcription factor for NADPH oxidase, which in turn, prompts inflammatory neovascularization [69]. From the bulk of these results, CTR1 and ATOX1 might be likely target to face cancer-associated angiogenesis.

Copper is also involved in the epithelial to mesenchymal transition (EMT), the mechanism necessary for cancer metastasization, conferring cells the gain of migratory and invasive properties [70]. During EMT, cancerous cells undergo molecular reprogramming, switch off the expression of genes coding for epithelial markers, such as E-cadherin and occludin, and turn on the expression of mesenchymal genes, i.e. N-cadherin and vimentin. The EMT genes are target of several transcription factors, including Snail, Twist, Slag and ZEB [70].

EMT also involves the intracellular copper-dependent amine-oxidase LOX. Indeed, processed and enzymatically active LOX stimulates Twist transcription, mediating the EMT of carcinoma cells [71]. Furthermore, interaction between copper-activated HIF-1α and HREs in turn transactivates its target genes involved in EMT regulation [59].

Indeed, in a hypoxia-induced EMT in a human breast cancer cell line (MCF-7), copper depletion inhibits the EMT *via* the down-regulation of the expression of the mesenchymal genes coding vimentin and fibronectin, which are under the control of the HIF1-α-Snail/Twist signaling pathway [72].

LOX was also identified as a putative interactor of MEMO1 (MEdiator of cell Motility 1) [73], a protein implicated in cell migration through modulation of cytoskeleton and formation of adhesion sites. Of note, in human breast cancer cells (MDA-MB-231) it was recently demonstrated that MEMO1 too is a copper-dependent redox enzyme [74]; it is intriguing that two copper-binding enzymes, LOX and MEMO1, both modulating the EMT process, may interact. MEMO1 acts *via* production of ROS, control of cell redox state and regulation of transcriptional pathways related to the EMT, the latter *via* interaction with IRS1 [75]. The role of copper on MEMO1 function and involvement in cancer deserves further investigation.

Several findings sustain the hypothesis that the membrane protein APP (Amyloid Precursor Protein) is deregulated in cancer and is implicated in cancer progression and metastasis [76]. APP shows an extracellular copper-binding domain at the N-terminus, and it is suggested to be involved in copper homeostasis. Copper is able to induce an increase in the expression of APP in non-cancerous cell line [77], and promotes the trafficking of APP from the Golgi to the plasma membrane [78]. Recent studies have shown that APP is fundamental for the EMT induction in brain metastatic prostate cancer DU145 cells [79]. In this paper, the authors demonstrated that treatment of DU145 cells with copper was sufficient to promote an increase in the APP expression levels, a significant reduction of the epithelial marker E-cadherin and the cells acquisition of a more elongated shape, hallmark of the acquisition of mesenchymal properties [79]. The APP-mediated induction of EMT depends not only on the presence of the intracellular domain of the protein (ICD) but also required the E1 copper-binding domain of APP [80].

3. Copper complexes in cancer therapy

From the set of evidence provided by the literature on the strong connection between copper-related proteins and the onset and progression of cancer, scientists have focused their efforts on the design and synthesis of molecules able to bind copper to be used in chemotherapy. These molecules have been used in many *in vitro* and *in vivo* studies as well as in clinical trials, showing their therapeutic efficacy in treating different types of cancer.

3.1. Traditional copper-binding compounds

Classical anticancer copper-binding molecules are classified into two main groups: copper chelators, which sequester copper ions from cells within the body [81], and copper ionophores, which, on the contrary, transport copper into cells increasing its intracellular levels and exerting cytotoxic effects through multiple pathways [34,82]. Several copper complexing species have been used for decades for the treatment of disorders other than cancer but, after discovering their anti-proliferative activity towards tumors, their use have been hijacked on the treatment of cancer. Among them are tetrathiomolybdate [83], disulfiram [84] and clioquinol [85].

The use of the selective copper chelator ammonium tetrathiomolybdate (TTM) it is well established for the treatment of Wilson's disease [83], but in the latest years it has been shown to exert an antineoplastic action by affecting copper modulation of the RAS/MAPK pathway [46,86,87]. TTM has been shown to be effective also in tumors harboring the oncogenic BRAF mutation ($BRAF^{V600E}$) and also affects the growth of those mutated melanomas that developed resistance to the inhibitors of both $BRAF^{V600E}$ and MEK1/2 [49,50]. Indeed, TTM is particularly well suited for long-term inhibition of the MAPK pathway in $BRAF^{V600E}$-positive papillary thyroid cancer (PTC), either in combination with current or emerging therapies and/or as a maintenance therapy [88].

Disulfiram (tetraethylthiuram disulfide, DSF) acts as a copper ionophore and increases intracellular bioavailable copper levels. It is a consolidate drug for the treatment of alcoholism, since it inhibits acetaldehyde dehydrogenase [84], and the first evidence on its efficacy in cancer treatment dates back to 1977 when it was used for an alcoholic patient affected by metastatic breast cancer [89]. DSF showed copper-dependent anticancer properties *in vitro* and *in vivo* and inhibits proliferation, migration and invasion of HCC (hepatocellular carcinoma cells) by impairing both NF-κB and TGFβ signaling [90]. In particular, it inhibits the nuclear translocation of NF-κB subunits and the expression of Smad4, leading to down-regulation of Snail and Slug, which contributed to the expression of genes inducing the EMT. Thus, DSF, in combination with copper, inhibits EMT [90]. In addition, the anti-metastatic and anti-angiogenic activity of DSF, when used in combination with copper, were also demonstrated in glioma, while copper alone had no effect [91].

Clioquinol (5-chloro-7-iodo-quinolin-8-ol, CQ), a derivative of chloroquine, was initially synthesized as an antimicrobial agent and was used to treat a range of diseases such as shigellosis, diarrhea, and intestinal amoebiasis [85,92]. In 2005, Ding and collaborators found that CQ was able to induce cell death by the activation of the apoptotic pathway in eight different human cancer cell lines [93]. It has been shown that the treatment of multiple human transformed (hyperplasic and carcinoma) prostate lines with CQ induced the nuclear translocation of the cytoplasmic XIAP, in a copper dependent manner. Indeed, the efficacy of the CQ treatment positively correlated with the extracellular copper levels [45]. Furthermore, Cao and colleagues demonstrated that CQ triggers also autophagy by inducing LC3 lipidation and autophagosome formation [94].

All three of these copper chelators have been employed in clinical trials. The trials with the most promising results are those concerning TTM. On the contrary, DSF showed limited effects on cancer patients, probably due to its metabolism. Indeed, once in the blood, DSF is metabolized to produce the active form of the drug, diethyldithiocarbamate (DDTC), and then diethyldithiomethylcarbamate and glucuronic acid. Thus, due to its turnover, DDTC is characterized by a low bioavailability. CQ was tested in only one human clinical trial in cancer patients without satisfactory results [95].

3.2. Novel copper-based anticancer agents

3.2.1. Copper-complexing compounds derived from plants

In the latest years the field of pharmacological research focused many of its energies on the identification of natural molecules that could exert anticancer effects or increase the anti-tumor activity of already known anticancer agents, with low side effects [96]. These compounds act as anti-oxidants but, in the presence of metals such as copper, act as pro-oxidants, catalyzing ROS formation and DNA degradation.

Many of naturally occurring polyphenols produced by plants are characterized by metal ion chelating properties. One of the leading compounds belonging to this class is curcumin. Curcumin, derived from the rhizomes of *Curcuma longa*, chelates copper and iron with high affinity. Indeed, the anticancer properties of curcumin are related to its activity as a negative regulator of several oncogenic molecules, i.e. the anti-apoptotic transcription factor AP-1, p53, MMPs (matrix metalloproteinases) and pro-inflammatory cytokines [97]. The efficacy of curcumin, as a copper chelator in the context of cancer, has been demonstrated also in a xenograft model of human lung carcinoma A549 cells. The oral administration of curcumin resulted in a decrease in the copper serum level correlated with an inhibition of tumor growth and angiogenesis [98]. Furthermore, copper supplementation has been demonstrated to increase the anti-cancer activity of curcumin in a panel of oral squamous cell carcinoma (OSCC) lines [99]. In 2013 Mandy et al.

reported the antitumoral effect of a Cu(II)-curcumin complex which exerts pro-oxidant effects generating ROS [100].

Coumarins are found in higher plants like Rutaceae and Umbelliferae and belong to the benzo-alfa-pyrones family. These molecules have been used as drug exploiting their anti-inflammatory, antimicrobial, antioxidant, anticoagulant and anticancer activities [101]. Coumarin-copper complexes have been shown to be effective in reducing the proliferation of an acute-T lymphoblastic leukemia and lung cancer cell lines, without any toxicity profile toward normal cells [102]. In particular, its cytotoxicity is correlated to the interaction of the carbonyl group of the coumarin moiety with DNA. However, the authors did not observe a specific correlation between the DNA binding constants and the cytotoxicity of the complex, suggesting that its biological activity could be related to other mechanisms than the DNA interaction [102].

The copper complex derived from S-benzyldithiocarbazate and 3-acetylcoumarin, namely $Cu(SBCM)_2$, was characterized by a multitarget anticancer activity in the human breast cancer cell line MDA-MB-231. It down-regulated the expression of mutant p53 thus making cells more sensitive to the effect of anticancer agents targeting oncogenic mutant p53 [103] It induced apoptotic cell death and finally promoted cell cycle block in the G2/M phase thus suggesting a possible development of this compound as cell cycle-targeting specific molecule [104].

Resveratrol is a polyphenolic stilbenoid, naturally present in the skin of red grapes and other fruits and berries, peanuts and also in the roots of Japanese knotweed. Following the observation of the ability of resveratrol-copper complexes (R-Cu) to cause DNA fragmentation of human lymphocytes, the use of this kind of complex was also proposed for cancer treatment [105]. In an interesting paper it has been shown a peculiar interaction between copper and resveratrol in exerting their cytotoxic activity. R-Cu caused DNA cleavage as result of hydroxyl radical formation. Interestingly, DNA and RNA cleavage and/or degrading activity of R-Cu increases as the ratio of R to Cu is increased and, finally, the activity was lost when the copper concentration was reduced to very low levels [106]. So far, this surprising finding remains unexplained and requires further investigation.

Oleuropein, the ester of hydroxytyrosol (3,4-dihydroxyphenylethanol) with glycosylated elenolic acid, is a phenolic compound belonging to the group of secoiridoids, found in the leaves, fruits and food derivatives from the olive tree *Olea europea*. It is well known the protective action of this molecule in neurodegenerative diseases, cardiovascular diseases, inflammation, viral or microbial infections, hypoglycemia, skin illnesses, osteoporosis and liver steatosis induced by high-fat diets [107]. Furthermore, oleuropein has been reported to modulate several oncogenic signaling pathways, in particular those modulated by the activity of MAPK. In HeLa cells oleuropein treatment induced JNK activation resulting in apoptotic cell death. In addition, in SKBR3 (breast cancer) cells following oleuropein treatment it has been shown the activation of ERK1/2 [108]. In a recent paper we have demonstrated that oleuropein forms complexes with copper characterized by the ratio two oleuropein molecules to one copper ion, as also suggested by molecular modelling analysis. We have also assayed the cytotoxic activity of oleuropein glycoside in SH-SY5Y human neuroblastoma cells finding that its efficacy is strictly correlated to the intracellular copper content. Therefore, the data obtained suggested a novel mechanism behind the anti-cancer effect of seicoiridoid polyphenols involving copper [109].

3.2.2. Autophagy inhibitors

New synthetic copper-based complexes have been developed to target the autophagic process. In human malignant glioma it has been shown that the copper complex casiopeina III-ia[Cu(4,4´ dimethyl-2,2 bipiridine)(acetoacetonate)]NO_3(Cas III-ia), induces cell death by autophagy and apoptosis, following the activation of ROS-dependent JNK signaling [110].

The inhibition of the autophagic signaling proved to be a winning strategy also in the treatment of HCC, using both Hep-G2 and Bel-7402 as cellular models. Indeed, di-2-pyridylhydrazone dithiocarbamate s-acetic acid (DpdtaA) and its copper complex (DpdtA-Cu) induced ROS-mediated inhibition of proliferation, p53 mediated apoptosis, lysosomal membrane permeabilization (LMP) and then autophagy [111]. Molecular docking simulation suggested that DpdtaA could disrupt the interaction between p53 and the protein deputed to the regulation of p53 level, i.e. the mouse double minute protein 2 (Mdm2). The p53 dependent reduction of MCF7 cells proliferation and apoptosis was achieved also with the use of a novel Isatin-Schiff base-Cu(II) complex [112].

3.2.3. Proteasome inhibitors

Another class of copper complexes potentially useful in cancer therapy is represented by the proteasome inhibitors. The ubiquitin-proteasome pathway (UPP) is responsible for targeting and proteolytic degradation of proteins and plays a central role in the regulation of cell cycle progression, signal transduction, differentiation, proliferation and apoptosis [113]. The 26S proteasome is a multicatalytic enzyme constituted by two subcomplexes: the 20S proteasome, representing the core particle, and a regulatory 19S particle, which may bind either to one or both sides of the core particle [114]. It has been already demonstrated the ability of the traditional copper-binding compounds (i.e. CQ, DSF and TTM) to target the proteasome system by either the production of copper-mediated oxidative damage to proteins or the formation of proteasome inhibitors once the compounds enter cancer cells. A series of copper-based inhibitors of proteasome have been already revised by Zhang and collaborators in 2017 [115].

Santoro and collaborators deeply investigated the ability of Cu(II) ions to inhibit the peptidase activities, assembly and gating mechanisms of the 20S proteasome [116]. They found that the Cu(II) ions inhibition of the 20S is independent from the core particle assembly but relies on the inhibition of the core particle gating mechanism, which was shifted toward the closed conformation. The data obtained in HeLa cells further demonstrated that Cu(II) ions inhibit proteasome peptidase activities and also promote, most likely trough the production of ROS, the disassembly of the 26S proteasome with a consequent increase of the amount of free 20S [116]. Chen et al. synthesized a hinokitiol copper complex (HK-Cu) that induced a huge accumulation of ubiquitinated proteins in human adenocarcinoma A549 cells and in the myelogenous leukemia K562 cells due to the strong inhibition of the activity of the 19S proteasomal deubiquitinating enzymes (DUBs) [117]. The accumulation of ubiquitinated proteins resulted in the induction of caspase-dependent apoptosis in both A549 and K562 cell lines [117].

3.2.4. Antiangiogenic copper-based complexes

As previously discussed, the involvement of copper in the modulation of angiogenesis has been suggested; however, to date, the effect of copper complexes on angiogenesis has not been deeply investigated. Recent studies found that the anti-angiogenic activity of cuprous oxide nanoparticles (**CO**-NPs) in HUVECs was mediated by the down-regulation of the VEGFR2 (vascular endothelial growth factor receptor-2) expression, both at the protein and mRNA level, without affecting the expression of VEGF nor VEGFR1 (vascular endothelial growth factor receptor-1) [118].

The modulation of the VEGF/VEGFR2 signaling axis has been also obtained by treating HUVEC with two novel mixed-ligand Cu(II)-based complexes [119]. The inhibition of angiogenesis relies on the down-regulation of the expressions of the crucial proteins FAK, Akt and Erk1/2 or their phosphorylated counterparts in the downstream of VEGF/VEGFR2 pathway [119]. Also, Shi and collaborators synthesize promising Cu(II) complexes, endorsed with antimetastatic and anti-angiogenic properties as demonstrated in HUVEC and B16F10 [120].

4. Copper machinery involvement incisplatin resistance

The high copper affinity transporter CTR1 was reported to be involved in the influx of cisplatin (CDDP) in tumor cells [10,121]. Platinum-based compounds (cisplatin, oxaliplatin and carboplatin) are widely used in the treatment of several malignancies (e. g. colorectal, ovarian, lung, head and neck, bladder, and testicular cancer). These drugs kill cells by forming DNA adducts and inducing programmed cell death [122]. However, one of the main problems associated with platinum-based chemotherapy, besides important side effects and toxicity, is the innate or acquired resistance of some tumor cell types. Resistance seems to be a multifactorial process, involving the intrinsic capability of the tumor cell to repair its DNA, or to prevent platinum drug accumulation, by limiting entrance or enhance elimination [123]. Decreased accumulation is indeed one of the most commonly observed features of resistant tumor cells, reported by both *in vitro* and *in vivo* studies and there are now multiple lines of evidence indicating that proteins involved in copper homeostasis are responsible for the import, intracellular distribution, and export of the various platinum drugs.

It has been suggested that the platinum resistance was related to inherent low levels of the copper transporter CTR1. Therefore, a strategy to overcome platinum drugs resistance is to induce an increase of CTR1 levels that, in clinical practice, is achieved by treatment with copper chelators (e.g. trientine dihydrochloride) [124]. To biochemically explain the possible correlation between CTR1 expression and platinum-based drugs transport, Liang and collaborators compared the mechanisms of CTR1-mediated transport of copper and CDDP [125]. The authors stably transfected small cell lung cancer (SCLC) cells with eight different CTR1 mutants. They found that the replacement of several methionine residues essential for CTR1-mediated copper transport (Met43, Met45, Met150, and Met154) lead to a reduced level of Cu(I) and CDDP transport, resulting in an increased resistance to the toxicities of copper and cisplatin. Furthermore, these mutations reduced maximal transport rates (V_{max}) for Cu(I) and CDDP but the reduction of K_m was observed only for Cu(I). However, the role of CTR1 in CDDP toxicity is controversial; some authors demonstrated that no increase of CDDP is observed in cervix squamous cell carcinoma A431 overexpressing CTR1, as well as no increased sensitivity to CDDP treatment [126]. In line with these results, knocking out CTR1 did not affect CDDP sensitivity [127]. Furthermore, more recently, knockout of CTR1, CTR2, ATOX1 and CCS was achieved in both human HEK-293 and ovarian carcinoma OVCAR8 cells by CRISPR-Cas9 genome editing. No increased sensitivity to CDDP was observed at all, suggesting that those proteins are not essential to the entrance of CDDP, at least in those cells [128].

The overcoming of the resistance to cisplatin and carboplatin was realized in human ovarian tumor xenografts by **co-**treatment with selenite, another drug used as an adjuvant in chemotherapy [129]. A possible mechanism to explain this effect may arise from the observation that selenite increases the expression of the antioxidant enzyme glutaredoxin 1 (Grx1) [130] which, in turn, increases CTR1, by the involvement of the transcription factor Sp1, as demonstrated in human neuroblastoma cells SH-SY5Y [131]. In exploratory experiments, we measured the protein level of Grx1, Sp1 and CTR1 upon treatment of HeLa cells and of H1299 (human non-small cell lung carcinoma) for 48 or 72 h with 2,5 micromolar selenite, which revealed to be moderately toxic to cells (up to 30%). Under these experimental conditions, no effect on protein levels of Grx1, or Sp1 or CTR1 was observed in HeLa cells (Fig. 3). Superimposable results were obtained for H1299 cells. Therefore, from these preliminary data, we cannot support that the possible increase of cisplatin sensitivity by selenite can be mediated by CTR1 protein enrichment. Indeed, phase I treatment with selenium and cisplatin in gynaecologic malignancy showed that selenium had no effect on carboplatin pharmacokinetics [132].

The involvement of the copper efflux transporters ATP7A and ATP7B in the acquisition of resistance to platinum drug treatment has been extensively discussed and revised by Li et al. and Lai et al. in 2018 [133,134]. The efflux transporters are able to sequester platinum in intracellular compartment or chelate platinum-based drugs through the binding to the CXXC motif forming stable and unreactive chelates [133,134]. Furthermore, intracellular copper levels could impair ATP7A and ATP7B activity, leading to platinum-drug resistance [124,135]. In the latest years, further evidences supported the role of these copper-ATPases in inducing platinum-drug resistance. Li et al. associate the *ATP7A* and *ATP7B* genetic polymorphisms with the clinical outcome and toxicity of platinum-based chemotherapy in NSCLC patients demonstrating that the *ATP7B* polymorphism rs9535826 is associated with the gastrointestinal toxicity of platinum-based chemotherapy. The results obtained suggested the possible use of this particular genotype as novel biomarkers for predicting the gastrointestinal toxicity of platinum chemotherapy in NSCLC patients [136]. In an *in vivo* mouse model, the deletion of *ATP7A* in tumorigenic mouse embryonic fibroblasts (MEFs) markedly reduced tumor growth and MEFs became hypersensitive to ROS generation induced by the increase in copper levels. Moreover, the deletion of *ATP7A* in MEFs increased cisplatin sensitivity both *in vitro* and *in vivo* [137]. In colorectal cancer, oxaliplatin (L-OHP) is the first line drug used for chemotherapy [138]. Reduced intracellular platinum accumulation has been identified as a major mechanism of L-OHP resistance [139]. It has been shown that the treatment of LoVo human colon (supraclavicular lymph node metastasis) cells with gambogic acid (GA), an active component of the traditional Chinese medicine, reversed L-OHP resistance decreasing ATP7A and ATP7B protein levels, resulting in increased intracellular platinum levels [140].

To better clarify the biochemistry of the platinum interaction with the copper-ATPases, Fand and colleagues produced 9 out of the 12 metal binding domains of the copper-ATPases and tested their reactivity towards cisplatin [141]. Interestingly, they showed that, in general, the platination rate of the MBDs was significantly improved, to a different extent regarding each MBDs, when they were previously loaded with Cu(I) [141]. Thus, the copper binding favors the interaction with cisplatin. It has been reported that cisplatin preferentially binds to the copper-binding site of ATOX1 and COX17 [142,143]. Of note, the copper removal from platinated MBDs is very slow, about 1 h, if compared with analogous reaction performed on copper-ATOX1 (~10 s) [144] thus suggesting that platinum binding caused just a perturbation of the Cu(I) coordination in the MBDs [141].

5. Conclusions

The research on the involvement of copper in cancer dates many years back, and revealed that this metal is involved in all aspect of cancer, from development to spreading. The results of those studies strongly suggest that this deregulation probably relies to the derangement of the protein system that surveys on copper homeostasis (CTR1, CCS, ATOX1, P-type ATPases).

More recently, studies on *in vivo* and *in vitro* models of different types of cancer have brought to light the interaction of copper with proteins participating to the cascades of signals leading to cell proliferation and cancer development. Copper may act at multiple levels, not only by directly binding to proteins involved in cancer progression, but also indirectly, by modulating their expression or release from cells. Copper is involved in the activation of the HIF-1, thus affecting ECM building by LOX and vascularization, by inducing the expression of GPER and VEGF. In particular, copper is required in the EMT, because it is an essential component of the CD44-Twist signaling axis, regulated by LOX, and cytoskeletal modulation and formation of adhesion sites, by means of MEMO1. The latter protein, due to the characteristics of its copper-binding site and the interconnections with other proteins, could prove to be a major new element in copper homeostasis, which can further sustain its implications in cancer. Therefore, novel components of the copper proteome have been identified and we begin to glimpse an

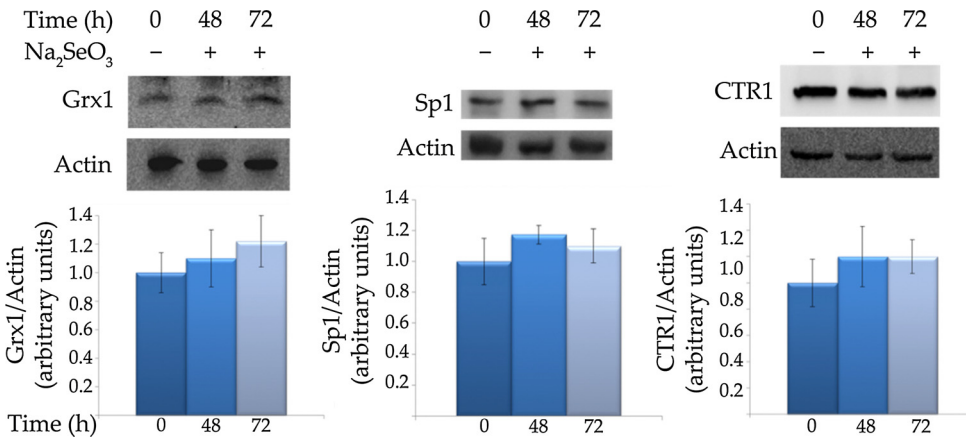

Fig. 3. Effects of selenite on the expression levels of Grx1, Sp1 and CTR1 in HeLa cells. Cells were treated with 2.5 μM selenite up to 72 h. Protein levels in cell extracts were determined by Western blot analysis. The antibodies used were: polyclonal anti-GRX1 (Santa Cruz Biotechnology, USA); polyclonal anti-CTR1 (Abcam, UK) and polyclonal anti-Sp1 (Cell Signaling, USA). Actin was used as a loading control (monoclonal, anti-actin, Sigma-Aldrich, USA). Densitometric analysis was performed with the ImageJ software. Data are presented as mean ± SD of three independent experiments.

exquisite interplay between them and the consolidated transporters and copper chaperones. Much research is required to better delineate the mechanisms involved in the loading of these proteins with copper within the cell. The impairment of their functions could be among the causes of cancer and the control over these proteins and their genes can be as new targets for cancer therapy.

The ongoing discoveries on the role of copper in cancer prompt the design and the synthesis of new copper-complexing agents; the properties of molecules produced by plants in binding copper and controlling its reactivity are intensely investigated, with the aim to find drugs for chemotherapy with lower side effects.

Overall, the investigation on the involvement of copper and cuproproteins in tumor development and metastatization, may lead to the discovery of novel targets for therapy and innovative therapeuthic agents.

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