ZINC AND GOLD COMPLEXES IN THE TREATMENT OF BREAST CANCER

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KOMPLEKSI CINKA I ZLATA U LEČENJU KARCINOMA DOJKE

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ABSTRACT

Metals are essential components in indispensable biochemical processes for living organisms. This review article highlights the metals zinc and gold in the development and treatment of breast cancer. Metal compounds offer many advantages as therapeutics due to their ability to coordinate ligands in a three-dimensional configuration. In aqueous solution, they form positively charged ions that can bind to negatively charged biological molecules. Metal complexes that contain metal ions such as zinc(II) and gold have received considerable attention as potential anticancer agents. Zinc is an essential trace element that plays a critical role in a wide range of cellular processes that include structural, signalling, catalytic and regulatory functions. Zinc acts as a key structural component in many proteins and enzymes, including transcription factors, cellular signalling proteins, and DNA repair enzymes, and perturbed levels of zinc in tissues may play a role in cancer aetiology and outcome. Unlike zinc, gold is feasible as a component of compounds for effective anticancer therapy. Some progress in anticancer therapy may include interactions between zinc and gold.

Keywords: *Zinc, gold complexes, breast cancer, anticancer therapy*

SAŽETAK

Metali su ključne komponente u svim važnim biohemijskim procesima u živim organizmima. Ovaj revijski članak opisuje najvažnije karakteristike određenih metala, cinka i zlata i njihovu ulogu u razvoju i lečenju karcinoma dojke. Kompleksi metala imaju značajne prednosti u odnosu na ostale terapeutike zbog sposobnosti da vezuju ligande i formiraju trodimenzionalne strukture. U vodenim rastvorima su u formi pozitivno naelektrisanih jona i tako mogu da vezuju negativno naelektrisane biomolekule. Metalni kompleksi koji sadrže jone metala kao što su cink(II) i zlato se intenzivno ispituju kao potencijalni antitumorski lekovi. Cink je esencijalni element koji ima ključnu ulogu u različitim procesima u ćeliji kojima se kontrolišu strukturne, signalne, katalitičke i regulatorne funkcije. Cink je sastavni deo mnogih proteina i enzima, uključujući transkripcione faktore, signalne proteine ćelije, enzime koji učestvuju u popravci DNA, a poremećena koncentracija cinka u tkivima može da ima ulogu u razvoju i ishodu tumora. Zlato se nalazi u sastavu različitih kompleksa koji pokazuju efikasan anititumorski odgovor. Neki od protokola koji se koriste za lečenje tumora uključuju kombinovanu primenu preparata koji sadrže cink i zlato.

Ključne reči: *Cink, kompleksi zlata, tumor dojke, antitumorski lekovi*

INTRODUCTION

According to the World Health Organization, breast cancer accounts for approximately 16% of all types of cancer deaths globally. It is the most frequently diagnosed solid tumour in women, and its incidence increases with age. Both molecular and genetic factors have been documented to play roles in the initiation and promotion of breast tissue oncogenesis (1). Among genetic factors, the most common cause is inherited mutation in the BRCA1 or BRCA2 genes (2). Deregulation of mechanisms that contribute to increased oxidative stress and the consequent genomic instability contribute to breast cancer development (3). The underlying mechanism may also rely on the ability of oestrogen and oestrogen metabolites to generate reactive oxygen species (ROS), which induce DNA synthesis, increased phosphorylation of kinases, and activation of transcription factors responsive to either oxidants (e.g., toxins,

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including metal compounds) or oestrogen. Environmental factors such as nutrition (obesity and alcohol consumption), smoking, and exposure to carcinogens (e.g., metal compounds) also play a decisive role in breast carcinogenesis. Deficiencies in key micronutrients may contribute to increased cellular stress and associated DNA damage (4-6). In addition, multiple reports show that metallic compounds can function as oestrogen disruptors (7), while other studies emphasize the connection between exposure to metals or metal compounds and breast cancer risk (8,9).

The present review discusses the association of specific metals, zinc and gold, with regard to their effects in contributing to breast cancer oncogenesis and to the beneficial effects of these metals in treating the same cancer.

ZINC TRANSPORTERS IN BREAST CANCER AND ZINC CYTOTOXICITY

Metals and metal compounds have been implicated in breast cancer biology in a few ways. They can be a possible risk factor for development of breast cancer, while on the other hand, their ability to induce cytotoxicity and apoptosis in breast cancer cells can be used for anticancer therapy, or they can be used as diagnostic markers. Zinc is involved in many aspects of cellular metabolism. It is required for the catalytic activity of enzymes, it plays roles in immune function, protein synthesis, wound healing, DNA synthesis, and cell division, and it is critical for the functioning of greater than 3000 transcription factors (10-12). The role of zinc in cell growth and division as well as basal homeostasis is of key importance. Zinc is needed for the stabilization of the nucleic acids DNA and RNA (13). In fact, all RNA polymerases (I, II, and III) are zinc metalloenzymes. Substitution of zinc has been shown to advantage DNA synthesis, while deficiency in this mineral inhibits DNA synthesis (14).

The participation of zinc in a number of physiological processes requires strict control of cellular zinc levels (15). Zinc cannot passively diffuse through the cell membrane and requires transporters for its passage (16,17). In addition, the intracellular distribution of zinc is tightly regulated by a family of proteins that control the uptake, efflux, and compartmentalization of zinc. There are three known families of zinc transporters, the Zrt-Irt-like proteins (ZIP family), the Cation Diffusion Facilitator family, often called the ZnT family, and the zinc-sensitizing MTs (18). The MTs play an important regulatory role in zinc uptake, storage, distribution, and release (19). Transporters of the ZIP family are responsible for the uptake of zinc from outside the cell into the cytoplasm and also contribute to zinc efflux from subcellular organelles into the cytoplasm. Members of the ZnT family of transporters, however, perform the opposite role, functioning in the efflux of zinc from the cytoplasm out of the cell, as well as in the translocation of zinc from the cytoplasm into organelles, effectively decreasing the cytosolic zinc concentration (20). The expression and cellular distribution of ZIPs and ZnTs are predominantly (but not always) regulated by changes in extracellular and intracellular zinc concentrations. The cellular distribution of zinc into organelles is precisely managed to provide the zinc concentration required by each cell compartment. There is evidence of ZnT and ZIP genetic polymorphisms, which could influence dietary zinc requirements and zinc metabolism (21).

Alterations of both cellular and serum zinc content have been shown in patients with breast cancer (22, 23). There is a 72% increase in zinc concentration in breast cancer tissue in comparison with normal tissue. This evidence regarding breast cancer is coupled with an observed reduction in serum zinc levels (24). In addition to the observed difference in zinc concentration within individual patients, cancerous breast cells tend to accumulate more zinc than ancillary non-cancerous breast cells (25). Significantly higher concentrations of zinc in breast cancer tissues compared to healthy breast tissue and lower levels in serum of patients with breast cancer seems to be due to altered expression of zinc transporters in breast cancer tissue (26-28).

The zinc transporter LIV-1 has been observed to be significant for breast cancer (29, 30). LIV-1 and ZIP10, both from the ZIP family, are associated with breast cancer metastasis to lymph nodes, and they may play a causal role in this process (31). The zinc transporter ZIP10 has been implicated in the migration and metastasis of breast cancer cells, and this invasive behaviour could be inhibited by the knockdown of ZIP10 expression (31). This study was consistent with findings from clinical samples showing that breast cancers with lymph node metastases expressed significantly higher levels of ZIP10 than those without lymph node metastases. Comparable results have been demonstrated with LIV-1 in HeLa cells (32).

ZIP6 is normally localized in the plasma membrane of mammary epithelial cells, where it imports zinc into the cytoplasm (33, 34). High levels of ZIP6 are found in metastatic breast cancer cells (35) and are positively correlated with lymph node metastasis (36), suggesting the possibility that it plays a role in tumour progression. A unique characteristic of ZIP6 is the highly conserved putative metalloprotease motif that resembles the active site found in matrix metalloproteinases (MMPs) (37). Increased expression of certain MMPs is associated with tumour growth, invasion, metastasis and angiogenesis and correlates with poor prognosis (38).

ZnT2 is abundantly expressed in the mammary gland and is over-expressed in ER+T47D cells (39). Hyperaccumulation of Zn in the malignant T47D breast tumour cells is correlated with ZnT2 overexpression and increased vesicular zinc pools. Further, attenuation of ZnT2 expression in malignant cells protects the metallothionein-null breast tumour cells from zinc-induced cytotoxicity by redirecting zinc into vesicular compartments (39). Because malignant breast cancer cells accumulate zinc, and exposure

to high levels of zinc activates apoptosis (40), mechanisms have evolved to protect cells against zinc-modulated cell death. Two genetic variants of ZnT2 have been characterized that may further implicate ZnT2 dysfunction in breast disease (41).

The broad involvement of zinc in biological processes indicates that aberrations in zinc status may play a significant role in cellular dysfunction, including the development and/or progression of cancer. Zinc is known to be essential for cell proliferation (42, 43) and may play a role in tumour growth (22-24). The effects of growth factors on proliferation are accompanied by an increase in the concentrations of labile zinc, whereas in the absence of zinc, cells are arrested in the S-phase, with cell proliferation being attenuated (10).

Opposing effects of exposure to zinc on cell survival have been described. Effects of high concentration of zinc in cells appear to be cell-type dependent. It has been reported that zinc induces apoptosis in different cells, including epithelial cells of prostate, ovaries, oesophagus, neurons, glial cells, and hepatoma cells. On the other hand, zinc has anti-apoptotic effects on breast and lung epithelial cells, renal cells, macrophages, lymphocytes, thymocytes, and pancreatic acinar cells (44). Further, it has been shown that exposure to low zinc levels induces apoptosis, whereas exposure to high zinc levels inhibits apoptosis (45). There is still no explanation for these apparently opposite actions of zinc. However, because of the critical role that zinc plays in biological systems and its unique properties, zinc has become a potential anticancer agent.

GOLD METALLOPROTEINS IN ANTICANCER THERAPY

Gold in solution exists as Au+ and Au3+. It has intriguing properties because gold does not react with water, air, oxygen, ozone, nitrogen, fluorine, hydrogen, sulfur, iodine or hydrogen sulfide under normal conditions.

An important issue, both theoretically and experimentally, is the interaction between gold and DNA. Recent experimental studies have shown that DNA bases, adenine (A), thymine (T), guanine (G), and cytosine (C), interact with Au surfaces in a specific and sequence-dependent manner. The relative binding affinities of these nucleobases for adsorption on polycrystalline Au films obey the following order: A > C ≥ G > T. Two key bonding ingredients underlie the base-gold and base pair-gold hybridizations: the anchoring, either of the Au-N or Au-O type, and the nonconventional N-H Au hydrogen bonding. The former is the leading bonding factor and results in stronger binding and coplanar coordination when the ring nitrogen atoms of the nucleobases are involved (46).

One of the most commonly proposed mechanisms for gold (III) compound-induced cytotoxicity is the induction of apoptosis by mitochondrial death pathways related to reactive oxygen species (ROS) (47). Gold(III) tetraphenylporphyrin downregulates the expression of genes involved in angiogenesis and inhibits formation of microvessels by epithelial cells. Further, gold(III) tetraphenylporphyrin has been shown to inhibit migration and invasion of nasopharyngeal carcinoma cells (48).

Several gold(I) and gold(III) complexes have shown *in vitro* anticancer properties against human cancer cell lines, including cell lines resistant to cisplatin. Cysteine-containing proteins appear to be likely targets for gold complexes due to the thiophilicity of gold. Among these proteins, Cys4 zinc finger domains have attracted significant attention because gold(I) and gold(III) complexes have been shown to inhibit poly(adenosine diphosphate ribose) polymerase-1, an essential protein involved in DNA repair and cancer resistance to chemotherapies (49).

Gold(III) complexes have shown promising results as anticancer agents due to their high cytotoxic effects on tumour cells both *in vitro* in tumour cell lines and *in vivo*, but they show reduced or even absent systemic or renal toxicity (50). In the presence of aurothioglucose, A549 human lung cancer cells exhibited a marked reduction in growth kinetics.

GOLD NANOPARTICLES IN THERAPY FOR BREAST CANCER

Ultrasmall gold nanoparticles (GNPs) consisting of a few to roughly one hundred gold atoms are promising candidates for delivery vehicles for anticancer drugs (51). Colloidal gold nanoparticles have great potential to overcome delivery limitations because of their biocompatibility, low toxicity, small size, and tuneable surface functionalities. If they are exposed to the biologicals in fluid, a protein adsorption layer forms around them. Gold nanoparticles have been coated with different biological agents including tumour necrosis factor, paclitaxel, and docetaxel (52-55). It was shown that compared with free or liposomal doxorubicin, doxorubicin-conjugated hollow gold nanoshells (HAuNSs) stimulated with an NIR laser enhanced eradication of tumours in vivo and were less cardiotoxic, most likely because the conjugated form was associated with less free doxorubicin in the blood (56).

A number of studies have shown that gold nanoparticles conjugated with antibodies are efficient in targeting and destroying cancerous tissue (57). A 4-component antibody-phthalocyanine-polyethylene glycol-gold nanoparticle conjugate is described as a potential drug for targeted photodynamic therapy of breast cancer. Gold nanoparticles, stabilized with a self-assembled layer of a zinc–phthalocyanine derivative (photosensitizer) under irradiation with visible red light efficiently produced cytotoxic singlet oxygen. It was shown that these gold nanoparticles, when conjugated with anti-HER2 monoclonal antibody, could be

effective photodynamic therapy agents for breast cancer cells that overexpress HER2 (58).

Another form of nanoparticles, Au-Fe3O4 conjugated with anti-HER2 monoclonal antibody and cisplatin, allowed target-specific delivery of platinum compounds to HER2-positive cells. Cisplatin conjugated to nanoparticles is released in endosomes after uptake of the conjugates, and it is considered that intracellular release of cisplatin is stimulated by the lower pH in endosomes (59). The higher release of cisplatin is followed by higher cytotoxicity (60).

CONCLUSION

Metals and metal compounds interfere with breast cancer in several means. Under specific conditions, they can represent possible risk factors for development of breast cancer, but their cytotoxicity might also have beneficial effects in inducing apoptosis and cytotoxicity in breast cancer cells. These include zinc- and gold-containing complexes, which have allowed significant progress in the pursuit of developing novel anticancer drugs. Advantages of metal-containing compounds are based on their ability to coordinate ligands in three-dimensional configurations, thus allowing functionalization of groups that can be tailored to defined molecular targets.

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