

Design and Biological Activity of Gold(I) Complexes for Cancer Therapy

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Abstract. Throughout the past few decades, the number of cancer cases has gradually risen on a year-on-year scale. For the purpose of battling cancer, various efficacious substances have been prepared, with a significant portion composed of platinum(II) complexes. However, the need to avoid the side effects that those drugs cause encouraged the invention of new metal-based drugs, among which gold(I) complexes are representative. This review will then introduce the respective features of platinum(II) and gold(I) antitumor complexes, afterwards analyze different theories on the mechanisms of action for gold(I) complexes, and finally describe the recent development of some potentially antitumor novel gold(I) complexes, including the use of different ligands, the influence from the substitution pattern and chirality of the same ligands, etc. Finally, several critical challenges were proposed. This review accelerates the rational design of gold(I)-based chemotherapeutics with improved safety and mechanism of action.

1 Introduction

Occurring in the form of vicious and exponential multiplication of some cells, cancer is a quite dreadful and mortal disease becoming increasingly prevalent. According to statistics from the National Cancer Center of China, the most frequent five vicious tumors are those that trigger cancer in the stomach, thyroid, lung, liver and colon-rectum. The number of deaths caused by cancer has, in recent years, undergone a sharp increase, as a result of low prognosis and easy metastasis. Regarding the trend of new cases of cancer, regardless of deaths or survivals in the end, they approximately attained 20 million in 2022, whereas 35 million people have been predicted to develop cancer within the year of 2050 alone [1]. To combat cancer, many treatment protocols have been invented and employed, such as chemotherapy, radiotherapy, surgical removal, and stem cell transplantation. Metal-based anticancer drugs, especially platinum (II) complexes (such as cisplatin, carboplatin and oxaliplatin), have become the cornerstone of chemotherapy. Initially restricted to treating testicular cancer, cisplatin has had its application extended and broadened to the treatment of bladder, cervical and ovarian cancers, while carboplatin has found application in treating ovarian cancer and lung cancer and oxaliplatin in pancreatic and colon cancer, respectively [2]. The covalent bonds between cisplatin and DNA are generally considered as the essential mechanism for the efficacy of these platinum-containing pharmaceuticals [2]. Nevertheless, conventional chemotherapy methods demonstrate some disadvantages, including non-selectivity, non-specificity (i.e., harming or even killing normal cells

around tumor cells), drug resistance [3]. In particular, during normal chemotherapy, the intake of anticancer drugs may cause toxic physiological side effects on the digestive system, the nervous system or the auditory system.

The need to circumvent those side effects forced the diversion of attention to other metal-based drugs, among which gold-containing ones are typical. The medical utilization of gold can date back a long time ago. In ancient China, the treatment of joint diseases, smallpox and skin ulcers has long involved gold compounds. When the 19th century approached an end, Robert Koch first observed $K[Au(CN)_2]$ to be effective in inhibiting tuberculosis in a culture disk environment. Later in the early 20th century, rheumatoid arthritis (RA) gradually came to be treated with auranofin and some gold-centered polymers, such as sodium aurothiomalate, aurothioglucose [4]. Auranofin was later found to have significant anti-proliferation activity and anti-tumor potential, which stimulated intensive research on gold complexes as new anticancer agents. In recent years, research of gold-containing substances as cancer suppressants/cures has been developed rapidly, with gold(I) cationic complexes representing an indispensable portion.

This review aims to summarize some “cutting edges” in gold(I) complexes employed or to be employed to fight against cancer. The interplay between gold cations and proteins from a mechanistic point of view was analyzed. The design strategies and chemical properties of various gold(I) complexes with different ligand structures were summarized. The antitumor activities, targets and application of these gold(I) complexes are described in detail. Finally, some challenges and

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opportunities for the future development of gold(I)-based anti-tumor drugs are prospected.

2 The interaction of gold cations with cancer cells

Gold(I) complexes curb the multiplication of cancer cells by binding to amino acids cysteine (Cys) and selenocysteine (Sec) within thioredoxin reductase (TrxR) protein. Auophilic sites, that is, sulfur atom and selenium atom, are intrinsic to Cys and Sec respectively and TrxR contains both amino acids, thus endowing itself with an affinity towards gold. Once binding to TrxR protein, gold(I) complexes will deactivate/denature it.

TrxR provides cancer cells with a protection from oxidative stress and resultant death within the cytoplasmic environment. To be specific, TrxR maintains at a low quantity the reactive oxygen species (ROS) produced in cells, and as a result, TrxR's being overexpressed further decreases the level of ROS and partly sustains the viability and rapid proliferation of cancer cells. Conversely, when TrxR is deactivated, ROS will accumulate to evoke apoptosis, i.e. the death of cells programmed by genes [3].

Gold(I) complexes can also induce the crosslink between DNA and proteins. Around 2014, Hu *et al.* found $[\text{Au}(\text{dppe})_2]\text{Cl}$, where dppe=1,2-bis-(diphenylphosphino)ethane, able to induce intracellular crosslink between DNA and protein, prevent DNA fracture and ultimately impede the proliferation of cancer cells [5]. The fracture of DNA chains partly underlies the deterioration of cancer because such fracture acts as a prerequisite for DNA duplication. Hence, the hindrance of DNA fracture will reduce the likelihood of cancer cells to replicate DNA and then reproduce themselves.

In addition, Hickey *et al.* conducted the synthesis of some gold(I) complexes targeting mitochondria. In the research, those gold(I) complexes were observed to exchange their nitrogen heterocyclic carbene (NHC) ligands for the amino acids Cys and Sec via two steps in the reaction environment. After exchanging the ligands, those gold(I) complexes became toxic to some breast cancer cells with high selectivity [6].

3 Gold(I) anticancer reagents

Ten electrons occupy the outermost electronic shell (the 5d orbital) of a gold(I) ion, rendering the shell a closed one. On the basis of hard-soft-base-soft theory, gold(I) ions are soft acids, with a much greater affinity towards soft bases than towards hard ones. Consequently, gold(I) ions are inclined to bond to cyanide, thiolates, iodide, phosphines and nitrogen heterocyclic carbenes (NHC's, abbreviated from now on) during the formation of gold(I) complexes. Besides satisfying such affinity, those groups binding to gold(I) ions (a.k.a. ligands) also stabilize gold ions. A gold(I) cation usually coordinates to two, three or four ligands, but most often two ligands.

3.1 Auranofin

The application of auranofin to battling cancer marks a milestone in the field. With a systematic name of (2,3,4,6-tetra-O-acetyl-1-thio- β -D-glucopyranosato-S) (triethylphosphine) gold(I), auranofin contains two ligands: a relatively lipophilic phosphine and a relatively hydrophilic polyester six-membered ring, as the molecular structure in Fig. 1 shows. Originally intended for the treatment of rheumatoid arthritis along with some other gold complexes, auranofin gradually displayed its versatility in the years that followed, exhibiting great potential as an antiviral, antiparasitic and antibacterial agent. Up till now, at least two mechanisms have been proposed for auranofin to take effect: the aforementioned inhibition of TrxR protein that modulates ROS in cells; the disruption of protein homeostasis by downregulating ubiquitin proteasome system (UPS). In recent days, auranofin is gradually and experimentally utilized in combination with other substances, including but not limited to vitamin C, L-ascorbate, trametinib and platinum-based drugs, etc. Such combination therapies under research intend to maximize curing effects, overcome drug resistance and minimize side effects [3].

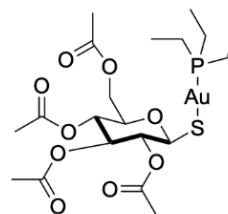


Fig. 1. The structure of auranofin.

3.2 NHC-gold(I) complexes

A carbene in the narrow chemical sense is a carbon atom that forms two bonds with other atoms or groups but has two lone (namely unshared) valence electrons. With less than eight electrons in its valence shell, this carbon atom is almost always intensely reactive and unstable, except when the two groups adjacent to it can stabilize it. NHC's belong to those special cases of stable carbenes, which are also termed persistent carbenes. "NHC" represents "nitrogen heterocyclic carbene", each possessing two nitrogen atoms that flank the carbene carbon atom and stabilize it via both electronic effects and steric effects.

The efficacy of some gold(I) complexes can be influenced by the substituent, chirality and identity of NHC's they bear.

In 2020, installation of different substituents on the phenyl ring of an NHC ligand (Fig. 2) enabled Gallati's group to observe substituent effects on the reactivity and cytotoxicity of multiple cancer cells. Specifically speaking, the 4-H and 4-CH₃ derivatives at very low concentrations were observed to have restrained cisplatin-resistant A2780cis ovarian cancer cells from multiplication. 4-OCH₃ and 4-F derivatives were found less competent at anti-proliferation of the cells, and the 3-F derivative was completely ineffective in preventing the proliferation, whatever the concentration was [7].

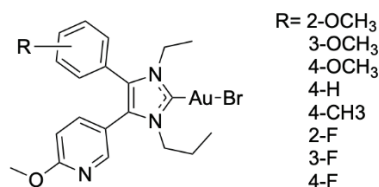


Fig. 2. Gold(I)-NHC complexes with different substituent groups (-R) [7].

When it comes to the influence of chirality on the effectiveness of anticancer compounds, different configurations can indeed cause distinct efficacy. Marra's group demonstrated that different configurations can impact the efficacy of mononuclear gold complexes as well, via surveys on the pair of enantiomers (Fig. 3). The *R*-isomer can stem the growth of MDA-MB-231 and MCF-7, two types of breast cancer cells, while the *S*-isomer only restrains MDA-MB-231 from development [8].

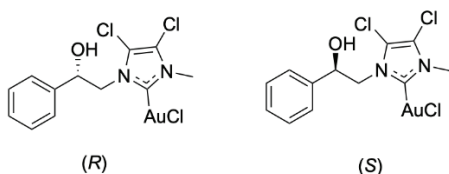


Fig. 3. The structures of a pair of enantiomers that exhibit varied efficacy [8].

In 2024, some thiocarboxylate-ligated gold(I)-NHC compounds were synthesized by Al-Buthabhak's group and were observed to be intensely cytotoxic to OVCAR-8, a type of ovarian cancer cells, with very low IC₅₀ values as proof [9]. In that exact same year, Ma and lab partners reported the success in the synthesis of some thiolate-ligated gold(I)-NHC complexes that incorporate two gold ions. The assay of those complexes displayed strong cytotoxicity to more than one type of cancer cells, some of which had already been proved resistant to cisplatin [10].

3.3 CAAC-gold(I) complexes

CAAC refers to "cyclic alkyl amino carbenes". Such a carbene can be prepared by substituting an alkyl group for one of the nitrogen atoms in an NHC. The constituent change as such enables CAAC to donate σ -electron density and meanwhile withdraw π -electron density better than NHC, and hence they are both excellent electrophiles and nucleophiles.

As early as 2017, Bertrand *et al.* synthesized a (CAAC)AuCl complex which carries a bulky adamantyl group. When tested for antiproliferative effects, with much lower IC₅₀ values, this complex displayed pronounced inhibitory effects on MCF-7 (cells that cause a kind of breast cancer) and on HL 60 (cells that trigger a type of leukemia), both of which proved resistant to cisplatin. Yet quite to the researchers' surprise, those complexes seemed hardly able to inhibit the activity of TrxR nor did they promote the formation of ROS, but an exact mechanism was not propounded [11].

In addition, Proetto's group also synthesized corresponding gold(I) complexes employing CAAC

ligands, as shown in Fig. 4. They observed that these complexes bind more specifically and selectively to cancer-related proteins. CAAC-gold(I) complexes are less likely to bind to non-cancerous proteins (50%) such as BSA, in comparison with gold(I)-NHC's and traditional auranofin (80%). Meanwhile, those complexes maintained a potent inhibition against TrxR [12].

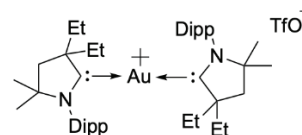


Fig. 4. The structure of CAAC-gold(I) complexes [12].

3.4 Phosphine-gold(I) complexes

Phosphines are also good nucleophiles and electron-donors, although their electronic properties are not so excellent as carbenes, but yet their neutral state of charge and the eight electrons in the valence shell (i.e. satisfying the octet rule) of their central phosphorus atoms both facilitate their preparation, storage and application. Thus, phosphines have been utilized as traditional ligands in metal coordination chemistry longer than NHC's. Furthermore, as introduced in section 3.1, auranofin has a phosphine ligand as well, and the reports on the effects of auranofin inspired the innovation of gold(I) complexes using alternative phosphine ligands.

In 2020, Zhang's group synthesized some alkynyl-bound gold(I)-phosphine complexes that are greatly effective in impeding metastasis (Fig. 5a). Not only can it inhibit mammalian TrxR intensely, it also retards the generation of ATP during cellular metabolism [13].

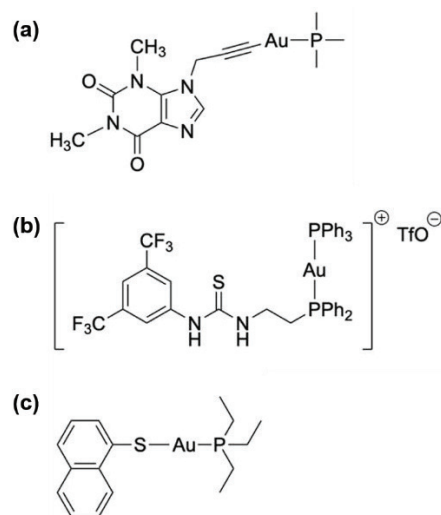


Fig. 5. Some effective phosphine-gold(I) complexes. (a) alkynyl-bound gold(I)-phosphine complexes [13], (b) gold(I) complexes bearing thiourea-connected phosphine ligands [14], (c) gold(I)-thiolate-phosphine complex [15].

In the following year, some gold(I) complexes bearing thiourea-connected phosphine ligands were prepared by Canudo-Barreras with his collaborators,

who found the one in Fig. 5b the most cytotoxic to HeLa cells and Jurkat cells (related to leukemia) at very small IC50 values [14].

A year later, Luo's group experimentally validated that lung cancer cells can be hindered from growing by a gold(I)-thiolate-phosphine complex, as presented in Fig. 5c, through the impairment of the mitochondria within malignantly-mutated lung cells [15].

4 Conclusion

As a highly promising category of anticancer agents that has emerged, gold(I) complexes appear distinct from traditional platinum-based drugs, primarily through their multifaceted mechanisms of action targeting vulnerabilities in cancer cells, such as the strong aurophilic affinity of the gold(I) cation for the TrxR active site, inducing DNA-protein crosslinks and ligands exchange. This review focuses on the anticancer activities, targets and application effects of various gold(I) complexes. The diverse ligand architecture profoundly shapes the biological activity. Auranofin inhibits TrxR and disrupts protein homeostasis, showing promise in combination therapies. NHC ligands offer exceptional tunability. Substituents, chirality, and nuclearity significantly enhance cytotoxicity and overcome resistance. CAAC ligands confer superior electronic properties, yielding complexes with remarkable potency against resistant cancers and significantly improved selectivity for cancer-related proteins over benign ones, while maintaining potent TrxR inhibition. Phosphine-based complexes beyond auranofin also show diverse efficacy, inhibiting metastasis/ATP production, exhibiting high cytotoxicity, or targeting mitochondria.

Future studies should delve deeper into synthesizing a wider array of gold(I) complexes and conducting systematic evaluations of their antitumor efficacy. Concurrently, several critical questions remain unresolved, such as elucidating the structure-activity relationship between the substitution pattern of a ligand and its efficacy. Besides, in the aspect of the mechanism of action, those theories are still quite controversial and therefore require further and more solid substantiation. With regards to new anticancer drugs, since almost all of them are still being investigated on cells or on non-human subjects, the results and performances may not be compelling and may not be consistent when those drugs are administered to human beings. As a consequence, the modification, improvement and optimization of the drugs should be accelerated so that clinical trials can be conducted as early as possible.

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