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Recent Advances in Gold(I) Complexes Based Biological Applications

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Abstract

The development of the synthesis of a wide range of Au(I) complexes reversibly promotes the advance in their practical usages, particularly, in biological applications. The formation of gold-sulfur rich protein adducts contributes to the cytotoxic nature of the gold compounds for chemotherapeutic approaches, while Au-Au interactions endow them with spectroscopic and luminescence properties. This article reviews that the recent five year progress for Au(I) complexes based biological applications, including the investigation of the development of new anticancer agents and antibacterial compounds, the application of biological imaging and the fabrication of novel sensors.

Keywords: Au(I) complexes, anticancer, antibacterial, biological imaging, sensors

1. Introduction

Au(I) complexes are attractive and key compounds in gold chemistry, bridges between elemental gold and gold nanomaterials. Advances in coordination chemistry enhance the development of Au(I) complexes and result in a variety of novel Au(I) complexes. The featured Au-Au bonds (aurophilicity) in Au(I) complexes give an fresh impetus to form unique fascinating structure and possess luminescence properties.

The intra- and inter- Au-Au binding interactions guarantee the stability of supramolecular structures, such as Au_{16} macrocycle[1], Au_{12} capsule and Au_{36} crown[2]. The aurophilic interaction of Au(I) complexes is also responsible for their unique photophysical properties. Recently, some excellent studies on Au(I) complexes have demonstrated that the special luminescence phenomenon of Au(I) complexes is assigned to aggregation induced emission (AIE)[3,4]. AIE, exactly opposite to traditional aggregation caused quenching (ACQ)[5], was firstly reported by Tang et.al in 2001[6]. They found that a series of propeller-shaped organic molecules emitted bright fluorescence in condensed phase, even in solid states. Then, the concept of AIE has permeated other materials, such as transition metal complexes. In 2012, Xie et.al firstly introduced AIE into Au(I) complexes, which are driven by aurophilic interaction and similarly emit in aggregation state[3]. Interestingly, different from typical organic molecular, Au-Au interactions endow Au(I) complexes with larger Stoker shifts, longer luminescence lifetimes and wavelength-tunable emissions. Due to metal centered triplet state, the emission of Au(I) complexes usually show phosphorescence properties. Moreover, the maximum emissions of Au(I) complexes change with the interactive distance of Au-Au[7].

Because of capabilities mentioned above, Au(I) complexes increasingly display practical potentials as promising candidates for bioluminescence materials. In the present review, we'll focus our discussions on the recent five years advances in bio-applications of Au(I) complexes, concluding to four directions, including anticancer, antibacterial, bioimaging and sensing applications. Besides applications of Au(I) complexes in imaging and sensing, we cover their utilities in antibacterial and anticancer, The former two directions derive from their cytotoxic nature, while the other two are mainly based on the luminescence properties. We also address the outlook and the challenge of future developments in this promising field.

2. Anticancer Study of Au(I) Complexes

Recently, a variety of Au(I) complexes have undergo the assessment of anticancer activity and the majority of them belongs to monometallic and bimetallic complexes. It's deduced that supermolecular or polymeric structures are avoided as the results of maintaining aqueous solubility and lipophilic moiety for the cell uptake at the same time. Therefore, usually the most common forms in therapeutic application are discrete molecular species.

Auranofin (thiolate-Au-PEt_3 complex, typical antiarthritic mononuclear Au(I) drug exhibits promising potentials as gold related anticancer agents[8]. Within this context, auranofin analogues (thiolate-Au-tertiary phosphine derivatives) have been explored to extend the variety of and improve the anticancer performance of Au(I) complexes. Gimeno et al. investigated a series of Au(I) complexes containing various bio-inspired amino acids modified ligands[9]. As shown in **Fig. 1**, they first obtained the precursor compound, nicotinic acid thiolate gold complex [Au(SpyCOOH)(PPh_3)] via the reaction of [AuCl(PPh_3)] with mercaptoniconitic acid. The acid moiety of this complex contributes to functionalization with biological groups such as the amino acids. The starting materials of amino acids coupling reaction are amino acids esters and the acids esters can return to acids species by LiOH induced hydrolysis. Therefore, the new exposed carboxylic acid moiety enables the prepared amino acids gold derivatives to continue to couple with a new amine. Owing to belonging to auranofin analogues, these thiolate Au(I) phosphine complexes containing biological molecules possess potent anticancer properties. A549 (lung carcinoma), Jurkat(T-cell leukaemia) and MiaPaca2 (pancreatic carcinoma) cytotoxicity assays demonstrate that the complexes can inhibit proliferation of tumor cells, with IC_{50} values as low as in the micromolar range. They also conducted similar assays with several structural modifications in order to establish the structure–activity relationship in this family of complexes, facilitating to the design of new and more potent

cytotoxic complexes[10]. Subsequently, they found that Au(I) complexes bearing cysteine-involving dipeptides exhibited high cytotoxicity, showing a very low IC_{50} values[11].

Similarly, Akim et al. replaced thiolate part with carbonimidothioates to prepare $Ph_3PAu[SC(OR) = NPh]$[12].They focused on the influence of the R substituents [R = Methyl(Me), Ethyl(Et) and isopropyl(iPr)] upon in vitro cytotoxicity. The compounds are hard to dissolve in water but are soluble in DMSO and acetonitrile. Noteworthily, Au-π interactions emerge in their crystal packing, which play an important role in supermolecular gold chemistry[13]. Those compounds exhibit significant cytotoxicity to the HT-29 cancer cell line. The results of Cytotoxicity assays show that the most active is the Me moiety containing derivative. Several normal cell apoptotic assays demonstrate that the cytotoxicity is responsible for apoptosis and both the extrinsic and intrinsic pathways of apoptosis have emerged. The Me containing compound stimulates the p73 gene, whereas each of Et and iPr activates the p53 gene.

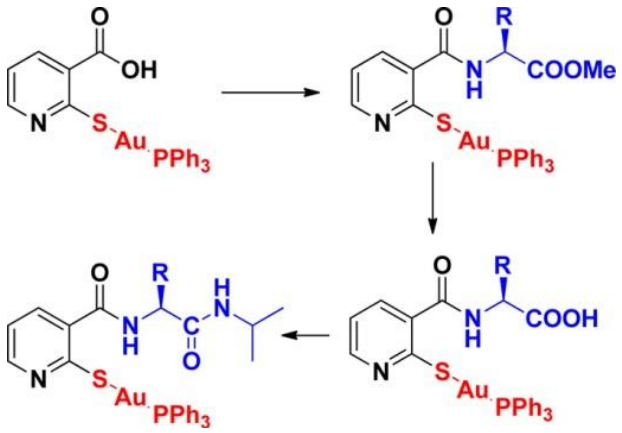

Figure 1. The synthetic scheme of Au(I) thiolate complexes containing amino acid moieties[9].

Biological activities of a series of DMSO-soluble aminophosphine thiolate Au(I) complexes [Au(SR)[2-(diphenylphosphinoamino)pyridine]] have been studied by Meireles et al[14]. Antitumor properties of these gold compounds have been tested in vitro against two tumor human cell lines, HeLa (cervical carcinoma) and MCF-7 (mastocarcinoma), using a metabolic activity test (MTT). These different R substitudes containing derivatives show a potent inhibition of thioredoxin reductase (TrxR) activity in HeLa cells. Additionally, the authors conducted a binding study of the Au(I) complexes with calf thymus (CT-) DNA and different bacterial DNAs. None significant structural changes occurr, although the interactions of complexes with CT-DNA have been verified.

Recently, Au(I) alkyne complexes gain increasing medical attentions for their impressive potentials in gold-based drugs. Ott and Rodríguez have investigated a range of DMF-soluble Au(I) alkyne Triphenylphosphine (PPh_3) complexes[15], specific targeting to TrxR and thus inhibiting tumor cells proliferation. Further, they examined biological properties of four binuclear Au(I) alkynyl complexes[16]. Their TrxR inhibition assays of different sizes of bridging ligands suggest a preference for the shorter ones. They also noted that those complexes exhibited strong cytotoxic activities against two different cultured tumor cell lines (MCF-7 and HT-29), albeit insignificant correlation with the activity of TrxR inhibition. Rodríguez reported a synthetic strategy of different Au(I) complexes with three kinds of propynyloxycoumarins[17]. In this study, they introduced water soluble phosphines to the compounds for the purpose of dissolving in water. Moreover, the following luminescence study indicates that the presence of Au(I) is responsible for the increase of coumarin phosphorescence emission. In addition, the neutral coumarins containing Au(I) complexes displayed strong cytotoxic effects on tumor cells, because of high TrxR inhibition (IC_{50} values below 0.1 μM).

As new candidates for chemotherapeutics, Au(I) N-heterocyclic carbene (NHC) complexes rapidly bring a wide interest as strong TrxR inhibitors constraining cell proliferation in a wide range of human malignant cell lines effectively. For the purpose of the design of anticancer bioorganometallics, Serebryanskaya synthesized a novel aminotriazole based NHC Au(I) complex[18]. Similarly, this compound also can

stimulate the cytotoxic effects in HT-29 and MDA-MB-231 cancer cells, as the result of TrxR targeting inhibition. Ott and Wölfl detailedly studied the mechanism of Au(I) NHC complexes induced cytotoxicity[19]. Their results reveal that Au(I) bis(NHC) complexes are able to cause pancreatic cancer cells apoptosis and the resulting cells death can be blocked by the usage of anti-oxidants, ASK1 siRNA or p38 inhibitor, suggesting that Au(I) NHC complexes promote cell damage and death mainly through the Trx-ASK1-p38 signal cascade. Their further results suggest that DNA damage may also associate with the compound induced cytotoxicity[20]. Dinda and Saha carefully examined the cytotoxicity of another NHC containing Au(I) complexes[21]. They found that the gold compound has a wide impact on cytotoxicity related signal ways and can trigger ROS, p53 dependent apoptosis and regulate the expression levels of pro- and anti-apoptotic factors (p53, p21, NF-κB, VEGF and MMP-9). Meanwhile, Hemmert et al. prepared new gold(I) complexes containing two 1-[2-(diethylamino) ethyl]imidazolydene ligands[22], which, particularly, showed a potent selectivity for cancer cells. Che et al. designed a binuclear Au(I) complex utilizing a bridging bis-NHC ligand to achieve both thiols stability and thiols reactivity[23]. The favorable thiols stability saves this binuclear Au(I) complex from the attacks of blood thiols, while thiols reactivity guarantees their ability to inhibit TrxR activity. This design can maintain high in vivo efficiency and indeed the in vivo studies reveal appreciable inhibitions of tumor growth in mice bearing HeLa xenograft or mouse B16-F10 melanoma without detectable side-effects supported by the following toxicology studies.

Coordination with other functional ligands pushes the chemotherapeutic development of gold drugs as well. Che et al. have shown that bis-thiolate derived Au(I) complexes can be attained through the use of thiourea (TU)[24]. The DMSO-soluble two-coordinate Au(I) complexes have been obtained using N,N'-disubstituted imidazolidine-2-thione and [Au(THT)Cl] (THT = tetrahydrothiophene). The nearest Au-Au distance in Au(I) TU complexes was over 3.29 A˚, suggesting the absence of significant intermolecular metal–metal interactions. This compound also exhibits significant cytotoxicity to cancer cells. Particularly, the gold complexes tightly bind TrxR and thus inhibit the activity of TrxR at nanomolar range. With ligand exchange reaction, Corbi et al. synthesized a new gold complex [$AuCN(C_3H_5NS_2)$] with 2-mercaptothiazoline (MTZ)[25]. The prepared complex is soluble in DMSO and be utilized for evaluation of the cytotoxic effect using HeLa cells, inducing 85% cell death at a level of 2.0 μmol/L. Berners-Price et al. successfully prepared a novel Au(I) phosphine complexes [Au(d2pype)2]Cl, [(d2pype = 1,2-bis(di-2-pyridylphosphinoethane)][26], showing selectively toxicity to tumorigenic cells. Further, untilizing nano-scale secondary ion mass spectrometry (NanoSIMS), they could visualize the distribution of gold in situ in human breast cancer cells in subcellular range for the first time. According their NanoSIMS ion map, 2 h treatment with [$Au(d2pype)_2$]Cl, the gold mainly distribute in sulfur-rich regions in the nucleus and cytoplasm, supporting the evidence of tight binding inhibition of sulfur-rich protein, such as TrxR.

3. Antibacterial study of Au(I) complexes

Due to the increasingly demands of antibacterial materials, new metallopharmaceutical compounds have been a new and interesting alternative way to develop effective antibacterial agents. Recently, Corbi et al. utilized potassium dicyanoaurate(I) as gold sources to synthesize a series of Au(I) complex of antibacterial activity via the synthetic strategy of ligand exchange. They selected four different biological function molecules including MTZ (a precursor for a variety of biologically active molecules)[25], rimantadine (a pharmaceutical agent)[27], N-acetyl-L-cysteine (a natural sulfur-containing amino acid)[28], ibuprofen (an anti-inflammatory drug utilized as a cyclooxygenase inhibitor)[29] as the ligands of Au(I) coordination, separately. The synthetic protocols are simple and convenient. After simple mixture of ligands and gold sources, the solutions

undergo gentle stirring in aqueous states at room temperature. The products are insoluble in water, possibly due to their polymeric structures, but they are easy to disperse in DMSO. Antibiogram assays indicate that all of the four complexes display effective antibacterial activity against both Gram-negative and Gram-positive microorganisms.

Water solubility has been considered of main interest in the development of both Au(I) NHC complexes as therapeutic agents[30]. Silbestri et al. prepared a variety of water-soluble Au(I) NHC complexes and investigated their antibacterial properties[30]. The antibacterial results by agar diffusion and broth macrodilution methods evince the antimicrobial ability of these complexes against both Gram- and Gram+ bacterial strains. Particularly, the antibacterial activity of some of these compounds is comparable with AgNO3. Gimeno et al. reported the synthesis of new Au(I) complexes with aminophosphane ligands and studied their antibacterial activity against Gram-negative and Escherichia coli and Gram-positive pathogens[31]. The bactericidal assays reveal that these compounds show a moderate antimicrobial activity on model Gram-negative and Gram-positive microorganisms and those in the absence of PPh3 moieties display significantly comparable bactericidal capabilities with the referencing antibiotics.

4. Bioimaging study of Au(I) complexes

In recent years, although a detailed insight into chemotherapeutic mechanisms of the Au(I) complexes is provided, the understanding of the cellular uptake and intracellular distribution of Au(I) complexes is lacked. Au(I) complexes have for long been known to possess metal-metal interaction generated luminescence properties, which are suitable for the biological imaging with confocal fluorescence microscopy (CFM). However, almost all of the earlier identified Au(I) complexes do not emit luminescence in the requisite solution states. Therefore, at present, the advances in cellular imaging of Au(I) complexes mainly focus on non-CFM mapping and CFM by the formation of fluorophores tagged Au(I) complexes or bimetallic cluster complexes.

As previously mentioned, Price et al. have technically applicated the combination of NanoSIMS and energy filtered transmission electron microscopy (EF-TEM) to mapping Au(I) complexes[26]. After administration of human breast adenocarcinoma cells with target gold compounds, NanoSIMS ion maps achieve visualization of the morphology of cells and distribution of gold synchronously, while EF-TEM can be utilized to observe cellular nuclear and mitochondrial morphology with excellent spatial resolution and its elemental maps are comparable with the results of NanoSIMS.

Although non-CFM maps exhibit potent advantages in Au(I) complexes imaging, the requirements of high-cost equipment are not available in most of laboratories. Therefore, synthesis of new luminescence emission Au(I) complexes seems to be a feasible way for gold compounds imaging. Coogan and Pope equiped alkynyl Au(I) complexes with fluorescent anthraquinone[32]. They prepared a series of mono- and bi-metallic Au(I) PPh_3 complexes bearing 1,2-, 1,4-, and 1,8-dialkynyloxyanthraquinone. Those compounds can well dissolve in DMSO, maintaining their anthraquinone based fluorescence. The administration of anthraquino containing Au(I) compounds can accordingly induce a significant cytotoxic behavior to MCF-7 carcinoma cell line. Then, CFM study with detection range from 530 to 580 nm is perform and the images show that the majority of gold compound distribute in cytoplasm, which allowed their successful access plasm organelles, supporting the gold-based drug cytotoxic mechanisms of mitochondrial inhibition.

Rhenmium(Re) complexes have also gained increasing attention for their promising use as imaging agents, due to their excellent photophysical properties and kinetic inertness. To trigger a synergic effect on both the excellent photophysical properties of Re complexes and the good anticancer activity of Au(I) complexes, Gimeno successfully developed a bi-heterometallic compound *fac*-[Re(bipy)$(CO)_3$(L-AuPPh_3)][33]. Cytotoxicity studies are

performed in human A549 lung cancer cells and the values of IC_{50} in heterometallic Re(I)/Au(I) derivatives group are over 10-fold less than their sister Re(I) complexes, suggesting the importance of the alkynyl–phosphine–gold staple for the purpose of efficient chemotherapeutic compounds. CFM records the distribution of the two Re involving luminescent complexes and the maps indicate that the bimetallic derivatives show a much wider interaction range of from mitochondria to the nucleus and even nucleolus than monometallic Re(I) species which only show general cytoplasmic mitochondrial accumulation. The imaging results indicate a completely different localization pattern for bimetallic species and also reveal that these species can serve as excellent partners in cell imaging and cancer therapy.

Ideally, the emission of functional complexes should be distinguished from the general short-lifetime biological background fluorescent emission. Fluorescence lifetime imaging microscopy (FLIM) could exactly fulfil that demand. The FLIM image is able to reveal the cellular uptake process of Au(I) complexes and provides information on changes in the intracellular microenvironment. Li et al. reported a cluster structure new heterometallic Ag(I)-Au(I) complex $[CAu_6Ag_2(dppy)_6](BF_4)_4$ with phosphorescent emissive features and excellent photostability[34]. This complex possesses a photoluminescent lifetime (~32 μs) which exactly conforms to the demands as a probe in applications of FLIM. They clearly observed that the courses of cellular uptake of the cluster complexes completed within 10 min through an energy dependent and non-endocytic way. The high levels of the complex in the nucleolus identified via inductively coupled plasma atomic emission spectroscopy (ICP-AES) and transmission electron microscopy coupled with an energy dispersive X-ray analysis (TEM-EDXA), indicate the possible accumulation of the gold compound in the nucleolus. These results give us a hint that solution state emission gold complexes possess promising potential for high revolution and qualitative imaging of nucleolus in living cells.

5. Sensing study of Au(I) complexes

In contract to the appreciable development of Au(I) complexes in anticancer study, recent sensing researches of Au(I) complexes, especially those obtained by organic synthesis, seems to be numbered. Probably, the poor aqueous solubility and the solution state induced quenching suppress their development in sensing application. However, the Au(I) compounds based sensors performing in organic solvent, such as vapor sensor, are still available. Catalano et al. prepared a heterometallic Au(I)-Cu(I) NHC complexes. The compounds can reversibly convert between MeCN- and MeOH-containing forms through ligand exchange reactions, exhibiting tunable luminescent vapochromic behavior. The featured luminescence properties allow the vapors sensing for different solvents, including MeCN, H_2O, MeOH, and Me_2CO. Mechanism assays demonstrate that the copper coordination number depending changes of Au(I)-Cu(I) closed-shell interaction are responsible for vapor-induced ligands exchange and resulting luminescent chromic behavior.

The fascinating Au-Au interaction induced luminescence phenomena are well-known facts that play an important part for supermolecular structure construction, self-assembly and luminescence properties. Albeit leaking in aqueous state, emissive properties of some Au(I) compounds in organic solvent still can be well preserved. Yam et al. developed a high selective Al^{3+} sensor based on a bis-alkynyl calix[4]arene Au(I) isocyanide complex[35]. The complex can well dissolve in CH_2Cl_2-MeCN mixture solvent and its emission band centers at 448-478 nm, originating from a mixture of triplet states arising from a metal-perturbed intra-ligand transition and ligand-to-ligand charge transfer transition. Upon introduction of Al^{3+}, the changes of the complexes in UV-vis absorption indicate the formation of a new chemical derivatives, probably Al^{3+} bearing adduct. The subsequent computational studies confirm the structure of the Al^{3+} binding Au(I) complex and the results show the trivalent Al^{3+} ion coordinates with two ether, two phenolic and two carbonyl oxygen atoms from the two amide moieties in a trigonal-

prismatic geometry shape, further identified by ^{1}H-NMR spectroscopy. The ion-induced structure changes accordingly facilitate the aurophilic interactions which produce a bright orange-red emission when exciting at the absorbance peak of 375 nm, suggesting a potent potential for Al^{3+} detection. The limit of detection (LOD) can arrive at 0.1 μM with excellent selectivity against common metal ions. Liu et al. reported a Hg^{2+} sensor based on the bimetallic alkyne-Au(I)-fluorobenzene complex that possesses AIE in MeCN-water mixture solution[36]. The yellowish-green AIE can be enhanced with sacrificing the solubility by the increase of the fragment of water. The emission can be quenched by Hg^{2+} selectively against conmen metal ions and provides luminescent decreasing response according to the amount of added Hg^{2+} in range of 0-20 μM. The quenching mechanism is reported to be ascribed to the de-aggregation induced by Hg^{2+}, supported by the results of dynamic light scattering measurements.

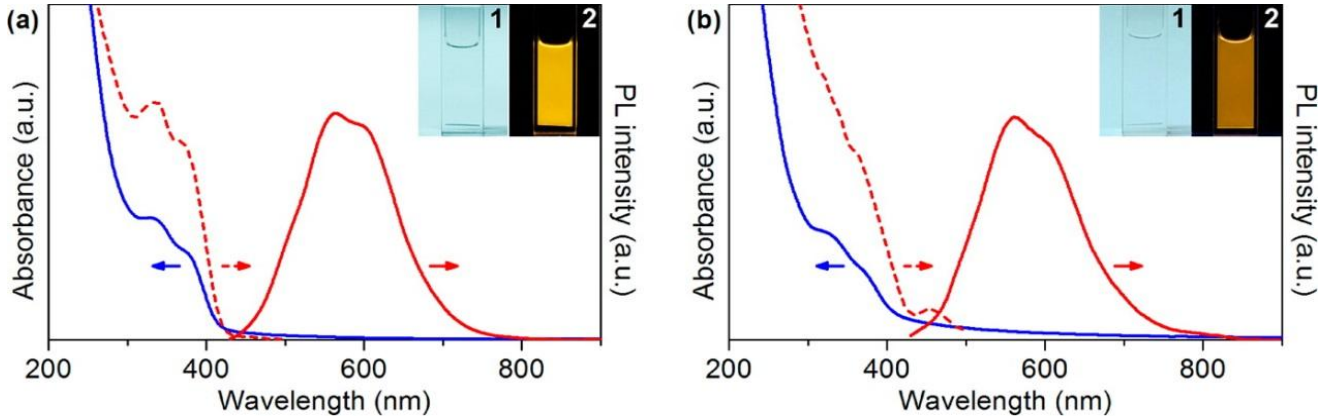

Figure 2. UV–vis absorption (solid blue lines), photoemission (solid red lines), and photoexcitation (dotted red lines) spectra of Au(I)–GSH complexes aggregated by (a) ethanol (95% ethanol by volume) and (b) Cd^{2+} ions. (Insets) Digital photos of aggregated complexes under (1) visible and (2) UV light[3].

Interestingly, recent growing organic solvent free synthesis (green synthesis) strategies have been proposed, particularly, in sensing application. Green synthesis has so far gained a wide range of attention due to its simple, safe and effective protocols. Lately, some papers reported that thiols could serve as both ligands and reductants in the synthesis of Au(I) complexes from Au(III) compounds, such as, aqueous soluble innoxious chloroauric acid, which avoid the utilization of cyanide coordinated gold sources. Through carefully controlling the amount of glutathione (GSH) and reaction temperature, Xie et al. are able to synthesis either mixed valence gold nanoclusters or Au(I) complexes from the same starting materials in aqueous solution[3]. The whole formation of Au(I)-GSH complexes involve two stages. The first stage is the reduction of Au(III) to Au(I) and the successive coordination of Au(I) by GSH. At this stage, the reacting pH was around the isoelectric point of GSH, resulting in the production of insoluble aggregates. The second stage is initiated by introducing NaOH to pH 7.0, comprising the dissolution and oligomerization of Au(I)-GSH complexes, respectively. The final products are mixtures of $Au_{10-12}SG_{10-12}$ species and the largest species is $[Au_{12}SG_{11}]^{+}$. Recalling the earlier mentioned AIE phenomenon, the Au(I)-GSH complexes emit a bright yellow light upon the addition of aggregative inducer, such as ethanol or metal cation, as shown in **Fig.2**. The augmentation of ethanol fragment in the water/ethanol mixture solution can trigger the intra- and inter-aggregation of the water-soluble Au(I)-GSH complexes and thus facilitate to the

Au-Au bonding interactions, resulting in metal-centered triplet state luminescence emission (~ 2 μs). Similarly, metal ions, for instance, Cd^{2+}, are able to chelate with the amino and carboxyl group of GSH ligands and the addition of Cd^{2+} accordingly lead to the formation of gold containing aggregates, emitting a bright yellow light. Ling and Cao developed a Pb^{2+} sensor with the usage of the Au(I)-GSH complexes[37]. Considering the interference by other transitional metal ion, they designed an indirect emission enhancement strategy that they first produced the AIE probe with the addition of Zn^{2+} into the Au(I)-GSH complexes solution and then the emission of AIE probe was further enhanced by the addition of target analyte, Pb^{2+}. The results of the AIE probe optimization experiments also demonstrate that the aggregation induced by Zn^{2+} is more stable, compared with other cationic inducer, such as Cd^{2+} and Pb^{2+}. With this luminescence probe, they constructed a Pb^{2+} sensor with linear range in concentration from 2 to 40 μM, with reliable performance in real water samples.

Besides GSH, cysteine, another endogenous thiol compound, can also be utilized as both the ligand and the reductant in the preparation of Au(I) complexes. Pei et al. successfully synthesized Au(I)–Cys complexes using similar methods[4]. They harvested $[Au_6Cys_7]^+$ as the main composition of the product, which also showed pH-dependent aqueous solubility. Analogous with EDTA chelator, Cys coordinated complexes allow a stronger interaction with a range of metal ion, including Ca^{2+}. Based on the AIE of Au(I)-Cys complexes via the introduction of Ca^{2+}, a label-free luminescence sensor for Ca^{2+} is developed. However, the carboxyl and amino group interaction with metal cation based probe shows poor selectivity for Ca^{2+} and several other divalent metal ions, including Ba^{2+},Cu^{2+}, Mg^{2+}, Pb^{2+} and Zn^{2+}. To remove the existing inference, riethylenetetramine(TETA) is employed as the making agent against Cu^{2+}, Pb^{2+} and Zn^{2+}. The following adjustment of pH to 11.5 with sulfuric acid avoids the inference from Mg^{2+} and Ba^{2+} via the formation of insoluble $Mg(OH)_2$ and $BaSO_4$ precipitates. Therefore, a super selective method for visual detection of Ca^{2+} is established with linear relationship in concentration range from 50 to 300 μM and appreciable feasibility of usage in real samples, for instant, lake water, fetal bovine serum and milk.

Some artificial thiols, such as 3-Mercapto-1,2,4-triazole (MTA), are similarly capable of reducing Au(III) to Au(I) and coordinating with Au(I) by the formation of oligomeric Au(I)-thiolates complexes. Due to better solubility of MTA in ethanol than water, Lu et al. mixed ethanol dissolving MTA with aqueous $HAuCl_4$, producing high quality of Au(I)-MTA complexes[38]. MALDI-TOF-MS assays demonstrate that the oligomeric $[Au(I)MTA]_3$ mainly constitute the products. Either in DMF solution state or in solid state, the gold compounds display a bright red emission with quantum yield of 38%. The probable electronic metallic triplet-state contributes to the phosphorescent emission of Au(I)-MTA complexes with a large Stokes shift of over 200 nm and an average lifetime of 10 μs at room temperature. These distinctive phosphorescent features of Au(I)-MTA complexes enable itself an excellent probe for cyanide detection. The LOD of this sensor can achieve a level of 80 nM with the linear relationship in concentration range from 0.16 to 50 μM. As for the selectivity, only S^{2-} interferes the phosphorescent signal of detection, which can be masked by introducing H_2O_2. Interestingly, in the concern of the solid state emission, they fabricated a phosphorescent macroporous film with Au(I) complexes for the first time and applicated this film sensor for colorimetric determination of cyanide in real samples, including red wine, coffee, juice, soil and even cassava. As above, solid or aggregates emission properties endow Au(I) complexes with promising potentials for film based sensor. Tedford et al. successfully fabricated a robust thin-film oxygen sensors by immobilization of a lipophilic, blue-green emissive polynuclear gold(I) complex, bis[m-(bis(diphenylphosphino)octadecylamine-P,P)] dichlorodigold(I), with oxygen permeable polystyrene and ormosil matrices[39]. The bright phosphorescence emission of the gold compound can be quenched by gaseous and dissolved oxygen. The functional film can stay in water

without leaching for a period of 8 h. Particularly, the oxygen induced phosphorescence quenching can be recovered completely with fast response time, indicating the fabrication of a recyclable and reversible thin-film sensor.

Besides aurophilic interaction based luminescence, other non-photophysics properties of Au(I) complexes can also be used to construct sensors. On accounts of the changeable chemical valence between Au(I) and Au(III) via reduction or oxidation, Srivastava et al. developed a electrochemistry sensor with imidazole-based NHC–Au(I) complexes for glucose analysis[40]. The mechanism of glucose detection can be concluded in two steps: Firstly, electrocatalytic oxidation from Au(I) to Au(III) occur at NHC–Au(I)-modified electrodes in the voltage increase procedure; And second step is the reduction from Au(III) to Au(I) by glucose. The NHC–Au(I)-modified electrode is anti-interference from other species coexisting in blood such as uric acid, and is further utilized to determine the blood glucose level in real serum samples with satisfied precision. Interestingly, based on the well-known specify-affinity metallophilic interaction between Hg(II) and Au(I), Zhang et al. developed a novel electrochemistry sensor modified with Au(I) alkanethiolate nanotubes for the Hg^{2+} detection[41]. Due to the super-hydrophobic properties, Au(I) alkanethiolate nanotubes modified glassy carbon electrode are encapsulated with nafion matrices for the enhancement of immobilizing stability. The novel Au(I) nanostructure based sensor with LOD of 0.5 nM exhibits two linear relationships in the concentration range of 1-100 nM and 100-1000 nM respectively. Due to the advantages of convenience, costeffectivity and fast detection, this electrochemical method possesses potent potentials for health related and environmental Hg^{2+} detection.

6. Conclusion and outlook

Last two decades witness great advances in synthesis and application of Au(I) complexes. This review focused and summarized recent five years efforts on the development of Au(I) complexes with various biological applications. Four selected biology related areas based on Au(I) complexes have been discussed and explored.

Gold-thiol containing protein interactions have been evidenced to be key issue for Au(I) complexes in regards of their chemotherapeutic effects. Prior to their binding to targets, chemical and biological stability should be guaranteed by the selection of suitable ligands. Besides traditional ligands, such as thiolate, phosphine and cyanide, several new members, including alkyne, NHC and fluorobenzence, are gaining more and more attention for their biological stability and structural richness. Meanwhile, the chemotherapeutic effects, mainly anticancer, have been detailed analyzed. DNA and protein assays demonstrate that the formation of gold-thiolate enzyme adducts are the direct reason for cells apoptosis and death. In order to holistic understanding the uptake of cells and subcellular distribution of gold compounds, plenty of imaging techniques have been adopted. The maps of NanoSIMS and EFTEM observe that gold complexes distribute in thiols-rich region in cytoplasm and nucleus. Indeed, anticancer capability of Au(I) has been careful explored and evidenced from cellular to subcellular levels. However, in vivo anticancer study of Au(I) complexes is quite insufficient and their side-effects still stay ambiguous. Great efforts should be exerted for a comprehensive biological assessment of Au(I) complexes.

As for the antibacterial activity, the recent attentions are focused on the materials preparation and routine antibacterial assay. However, the antibacterial mechanism is rarely concerned, thus limiting the development of the Au(I) complexes in antibacterial. In addition, among the antibacterial technologies based on Au(I) complexes, simple solution mixture is the most frequent method. In this regard, various nanotechnologies and nanomaterials, such as micro-/nano-carriers, can be applied to improve the antibacterial activities.

The advances of Au(I) complexes in imaging, especially in CFM, are associated with ligands. Either organic or metallic fluorophores can facilitate to the usage of CFM and thus the distribution of gold compounds can be observed.

However, the imaging studies based on the emission from gold are quite rare, although Au(I) complexes are able to emit phosphorescence featured light with high quantum yields, as the results of Au-Au binding interaction. The scarcity for the Au(I) moiety induced luminescence imaging are possibly ascribe to dissolving state associated quenching of Au(I) complexes. Therefore, the synthesis of Au(I) complexes capable of aqueous emission is essential for the development of Au(I) complexes in bioimaging. In this concern, di- and poly- nuclear gold compounds could be promising candidates for in vivo and in vitro bioimaging. The multinuclear Au(I) complexes can form cluster accumulation structure or intra-aggregates induced by small molecules, which shall not increase the size of the complexes and resulting produce insoluble precipitates.

Recent Au(I) complexes based sensing technologies are mainly applicated in metal ion detection. Indeed, applausively, the AIE concept has been introduced to the Au-Au bonding generated emission, which extend the understanding and application of Au(I) complexes in sensing design. However, rare reports involve the detection of physiological small molecule and other important health science related compounds. Therefore, the novel materials and design should be proposed in order to fulfill the demands for sensing a wider range of analytes.

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