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Recent advances in discrete Cu complexes for enhanced chemodynamic therapy

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Since the concept of metal ion stimulation-mediated chemodynamic therapy was proposed by Bu and Shi's group in 2016, increasing attention has been directed toward the fabrication of efficient, safe and stable Fenton/Fenton-like catalysts to advance clinical translation. In particular, metal-based complexes with inherent metal catalytic centers have received extensive attention as potential alternatives/complements for traditional CDT agents. Among them, copper-based complexes, which possess excellent redox properties, extensive adaptability and abundant availability, enable the efficient generation of ROS through Fenton-like reactions in CDT, thereby causing oxidative damage to lipids, proteins, and DNA in cancer cells. In this brief review, we summarize the recent progress on various discrete copper-based metal complexes aimed at enhancing the therapeutic efficacy of CDT as well as their application in combination therapy. We hope that this review will attract active attention toward metal complexes in advancing more accurate and efficient chemodynamic therapy and encourage further in-depth research to facilitate clinical translation.

Chemodynamic therapy (CDT), characterized by minimal invasiveness and high tumor specificity, has emerged as a promising therapeutic strategy in the past few decades.[1] It utilizes Fenton/Fenton-like reactions for the conversion of intratumoral endogenous overexpressed H_2O_2 into the hypertoxic hydroxyl radical ($^{\bullet}OH$), which induces lipid peroxidation and DNA damage and ultimately leads to cell death.[2] In order to improve the efficiency of the Fenton/Fenton-like reaction mediated by different metal centers, various CDT agents containing different metal centers (iron, copper, manganese, *etc.*) have been widely studied and reported.[3–5] Currently, the increasing interest in developing and evaluating nanomaterials for CDT is largely attributed to their multi-component functional modification, which may achieve the regulation of physiological function, treatment and imaging.[6–8] Compared to multifunctional nanomaterials, metal-based complexes show inherent advantages in CDT as they do not require the introduction of extra Fenton/Fenton-like response metal centers.[9,10] Additionally, due to their precise formulas, both the structure and physicochemical properties are controllable in CDT. Furthermore, the synthesis, purification and characterization of metal-based complexes are straightforward and highly reproducible, ensuring that uncertain components are not present in the structure, which may cause unpredictable risks.[11] More importantly, these metal complexes can be optimized by controllable and reasonable structural design using a wide variety of functional ligands to obtain potential CDT agents with excellent physical and chemical properties, which can enhance the therapeutic effect and safety.[12] Recently, several Cu-based nanoclusters and MOF materials have also been reported as potential excellent therapeutic agents and drug carriers in CDT.[13–16] In this brief review, we mainly focus on the recent advances in discrete Cu-based complexes for enhanced CDT. Additionally, we address the issues and challenges associated with the future development of metal-based CDT.

Targeted delivery enhances CDT

Although the overexpression of hydrogen peroxide as one of the basic characteristics of the tumor microenvironment endows CDT with higher specificity toward tumors, achieving a higher uptake of CDT agents by tumor cells is of significant importance. In other words, introducing high-affinity ligands enables cell-specific recognition and binding to Fenton/Fenton-like metal center complexes, which can enhance the delivery of CDT agents to the tumor cells, thereby improving the therapeutic efficiency.[17–19] Owing to cancer cells with rapidly dividing nature and voracious appetite for vitamins, our group prepared a simple and feasible atom-precise biotin (vitamin H) ligand-directed biotinylated Cu(I)-based complex

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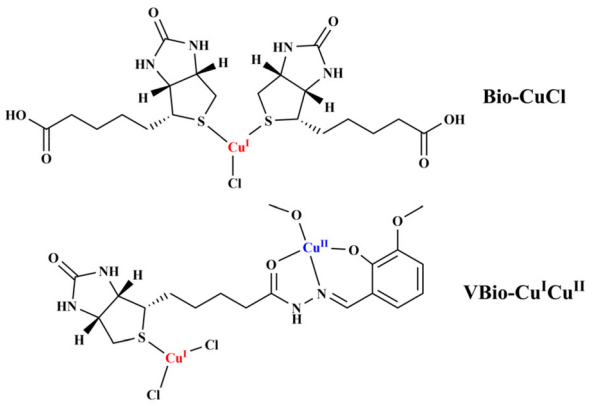

Fig. 1 Chemical structure of **Bio-CuCl** and **VBio-Cu^{I}Cu^{II}**.

$[CuCl(Biotin)_2]\cdot 2H_2O$ (**Bio-CuCl**, Fig. 1).[20] The Cu(I) moiety can catalyse the generation of $^{\bullet}OH$ *via* a Fenton-like reaction, while the biotin moiety enables **Bio-CuCl** to be specifically accumulated in biotin receptor positive tumor cells. It cannot be ignored that the overexpressed glutathione (GSH, the strong reducibility in the tumor cellular antioxidant defense system) would significantly scavenge the generated $^{\bullet}OH$ produced by the CDT agents. Therefore, it is necessary for CDT agents to simultaneously achieve high Fenton-like reaction efficiency and favourable depletion of intracellular GSH. On this basis, a biotinylated mixed-valence (both monovalent and divalent) copper complex $[Cu^{I}Cu^{II}Cl_2(VBio)]\cdot CH_3OH$ (**VBio-Cu^{I}Cu^{II}**, VBio = deprotonated *O*-vanillin biotinylhydrazone, Fig. 1) was rationally constructed and obtained by our group.[21] In this multifunctional CDT agent, the biotin unit offers good targeting to receptor-positive cancer cells. Cu(I) could generate hypertoxic $^{\bullet}OH$ directly through the Fenton-like reaction with hydrogen peroxide in the tumor cells (eqn (1)). Simultaneously, the Cu(II)-mediated reduction of intracellular GSH levels was accompanied by more Cu(I) production (eqn (2)), resulting in an enhanced killing of the tumor cells and inhibition of tumor growth.

$$Cu(I) + H_2O_2 \rightarrow Cu(II) + {}^{\bullet}OH + OH^{-} \quad (1)$$

$$Cu(II) + GSH \rightarrow Cu(I) + GSSG \quad (2)$$

Optimizing the tumor microenvironment enhances CDT

As the reaction substrate of the Fenton/Fenton-like reaction, the concentration of H_2O_2 directly affects the formation of $^{\bullet}OH$. In the limited concentration range of endogenous H_2O_2, retarding the ineffective decomposition of H_2O_2 in tumors is particularly important for increasing H_2O_2 to provide sufficient raw materials for the Fenton/Fenton-like reaction.[22] Catalase (CAT) is one of the essential enzymes of peroxisomes. When the endogenous level of H_2O_2 is high, CAT will convert H_2O_2 into H_2O and O_2; thus, inhibiting the CAT activity will increase the utilization rate of H_2O_2 within a certain range.[23] Inspired by this, Shen *et al.* prepared some copper(II) complexes with halogenated quinoline Schiff base derivatives (Fig. 2),[24] among which $Cu(L^4)_2$ and $Cu(L^{10})_2$ could react with GSH to release Fenton-like Cu(I) to catalyse the generation of $^{\bullet}OH$ from intracellular H_2O_2. In addition, $Cu(L^4)_2$ and $Cu(L^{10})_2$ could act as inhibitors to suppress the CAT activity, thus retarding the decomposition of H_2O_2 in tumors for enhanced CDT. Furthermore, it is worth noting that after the modification of the ligand structure, $Cu(L^{10})_2$ demonstrated more desirable pharmacokinetic properties, including longer half-life and higher maximal plasma concentration.

Meanwhile, apart from inhibiting the decomposition of H_2O_2, considering that H_2O_2 is mainly produced and enriched in the tumor mitochondria,[25,26] the CDT agents can also be directly delivered to the mitochondria; thus, increasing the contact with H_2O_2 can also enhance CDT to a certain extent.[27,28] Based on the above, our group designed and synthesized a cinnamaldehyde-derived copper(I) complex (**Cin-OD-Cu**, Fig. 2).[29] When taken up by the A2780 tumor cells, **Cin-OD-Cu** could continuously accumulate in the mitochondria and act as a high-efficiency Fenton-like agents to convert endogenous H_2O_2 into $^{\bullet}OH$. Conversely, the produced ROS cause irreversible oxidative damage to the mitochondria of A2780 cancer cells, decreasing the mitochondrial membrane potential, activating caspase 3/9, and ultimately inducing cell death *in vitro* and *in vivo*. This kind of complex obtained by the reasonable modification of the ligand can not only increase the probability of contact with H_2O_2 more accurately but also effectively shorten the distance between the position where $^{\bullet}OH$ is generated and the biological macromolecules to improve the attacking efficiency of $^{\bullet}OH$ toward biological macromolecules and ultimately achieving enhanced CDT efficiency. Besides, a triphenylphosphine (Ph_3P)-modified tetra-nuclear Cu(I) complex was also constructed and synthesized, which exhibited enhanced anti-tumor abilities through CDT owing to its higher copper content.[30]

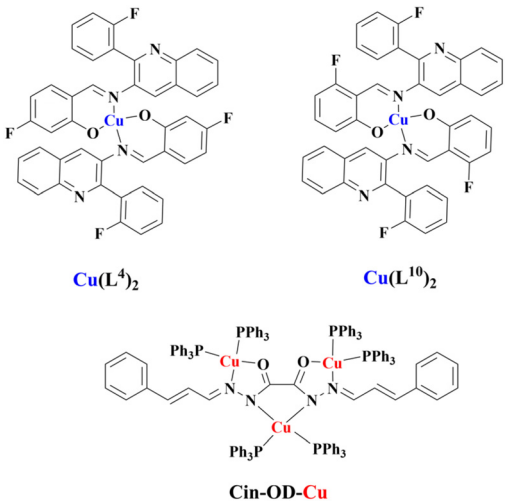

Fig. 2 Chemical structure of **Cu(L^4)$_2$**, **Cu(L^{10})$_2$** and **Cin-OD-Cu**.

Bimetallic center synergistically enhances CDT

The success of metal-based CDT agents mainly depends on the rational choice of an organic ligand, which plays an important role in modifying the targeting properties and reducing the adverse effects in order to facilitate positive impacts in CDT. On the other hand, owing to the synergistic effect of the two metal atoms, mixed bimetallic complexes always reveal better optical, chemical and catalytic properties than monometallic complexes.[31,32] Taking the Fe(II)-mediated Fenton reaction as an example, single Fe(II) with higher catalytic activity will inevitably be oxidized into Fe(III) by an endogenous oxidizing agent.[33] However, the slow transformation rate of Fe(III) to Fe(II) greatly restricts the performance of the catalyst and hinders the further application of CDT.[34] To address these issues, the introduction of Cu(I) into the aforementioned system can thermodynamically facilitate the charge transfer between Fe(III) and Fe(II) in the Fenton reaction; the reduction of Fe(III) by Cu(I) (eqn (4)) (*i.e.*, synergistic catalytic effect) can also facilitate the regeneration of Fe(II).[35–37]

$$\mathrm{Fe(III) + Cu(I) \rightarrow Fe(II) + Cu(II)} \quad (3)$$

$$\mathrm{Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\bullet}OH + OH^-} \quad (4)$$

Based on the above, our group constructed and synthesized an atom-accurate ferrocene-modified Cu(I) complex (**Fc-OD-Cu**).[38] For comparison, the copper complex (**Ba-OD-Cu**) and ferrocene complex (**Fc-OD**) containing a single metal center were also synthesized (Fig. 3). The results of extracellular and intracellular $^{\bullet}OH$ generation experiments results showed that **Fc-OD-Cu** with a hetero-metallic Fenton catalytic center has better $^{\bullet}OH$ generation ability than **Ba-OD-Cu** and **Fc-OD** with a single metal center. *In vitro* and *in vivo* experiments confirmed that **Fc-OD-Cu** could remarkably inhibit the growth of Hep-G2 cells and significantly ablate the intracellular tumors due to the enhanced Fenton effect. On the other hand, due to different metal properties, metal-based CDT agents, involving two metal centers, could serve not only as the GSH-depleted agent for reducing the intracellular GSH level but also as the Fenton/Fenton-like catalyst for inducing the apoptosis of tumor cells by the produced highly toxic $^{\bullet}OH$. Based on this, Cao *et al.* first reported an Mn–Cu bimetallic **complex 1** (Fig. 3) for enhancing antitumor CDT efficacy.[39] **Complex 1** could produce $^{\bullet}OH$ through a Fenton-like reaction induced by the Mn(II) metal center. Simultaneously, the intracellular GSH level was decreased by the Cu(II) center. Consequently, **complex 1** exhibited an enhanced CDT effect on 4T1, HepG2, A549 and MCF7 cancer cells, and the IC_{50} value was even lower than that of the anti-cancer chemotherapy drug cisplatin.

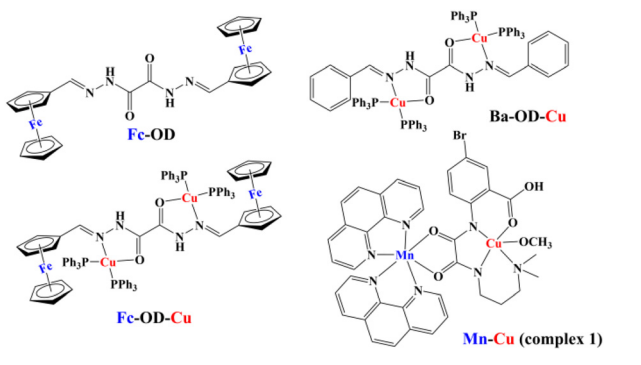

Fig. 3 Chemical structure of **Fc-OD**, **Ba-OD-Cu**, **Fc-OD-Cu** and **complex 1**.

Collaborative therapy enhances CDT

CDT can also be used in combination with other therapies, such as photodynamic therapy (PDT),[40,41] photothermal therapy (PTT),[42,43] and sonodynamic therapy (SDT).[44,45] Integrating CDT and other therapies into one system could generate much more ROS and reduce the injected dose. More importantly, the combination of CDT with other treatments can bring multi-killing mechanisms to overcome a series of undesirable escape mechanisms and/or drug resistance mechanisms and realize the conspicuous "1 + 1 > 2" synergy therapeutic effects in the overall cancer treatment.

Kim *et al.* firstly reported a Cu(II)-BODIPY PS complex (**CA9-BPS-Cu(II)**, Fig. 4)[46] containing a carbonic anhydrase-9-targeting ligand, Acetazolamide and demonstrated its efficacy in promoting a synergistic CDT/PDT effect with cancer stem cells targeting to enhance cancer therapy. The results of the *in vitro* cytotoxicity study showed that **CA9-BPS-Cu(II)** increased the cytotoxicity of MDAMB-231 in a dose-dependent manner under 660 nm laser irradiation, which was attributed to the Cu(I)-mediated production of ROS, a CDT effect enhanced by PDT-induced ROS production and, in part, by copper-catalysed glutathione depletion. In addition, the effectiveness of **CA9-BPS-Cu(II)** was also demonstrated in a xenograft mouse tumor model. Inspired by the above combination therapy, our group synthesized an atomically precise cinnamaldehyde-derived metal–organic Cu(I) complex (**DC-OD-Cu**, Fig. 4) for CDT/PDT combination cancer therapy.[47] **DC-OD-Cu** could preferentially accumulate in the mitochondria of HeLa cells due to the mitochondria-targeting ability of triphenylphosphine, which was accompanied by the generation of large amounts of $^{\bullet}OH$ through Cu(I)-mediated Fenton-like reactions. Meanwhile,

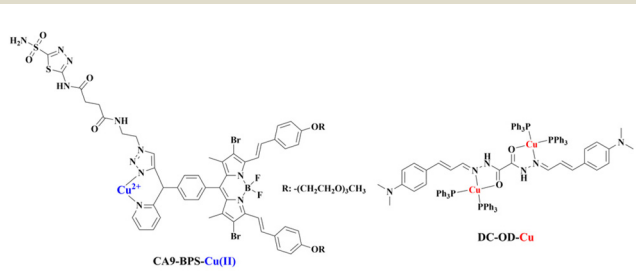

Fig. 4 Chemical structure of **CA9-BPS-Cu(II)** and **DC-OD-Cu**.

Table 1 Recent summary of Cu-based complexes applied for enhanced CDT

Cu-based complex	Strategy to improve CDT efficiency	Cell line(s)	IC_{50} (μM) or Cell viability	Ref.
Bio-CuCl	Tumor targeting enhanced CDT	HeLa	—	20
VBio-$Cu^{I}Cu^{II}$	Tumor targeting/GSH-depletion enhanced CDT	4T1	~28.1% (25 μM)	21
$Cu(L^{10})_2$	Inhibit H_2O_2 decomposition enhanced CDT	T24	9.6 ± 0.9	24
Cin-OD-Cu	Mitochondria-target enhanced CDT	A2780	1.38 ± 0.21	29
Fc-OD-Cu	Catalytic center optimization enhanced CDT	Hep-G2	~55% (5 μM)	38
Complex 1	Catalytic center optimization/downregulating reduced substances enhanced CDT	A549	2.29 ± 0.083	39
CA9-BPS-Cu(II)	Photo-assisted enhanced CDT	MDAMB-231	~30% (30 μM)	46
HA@Cy-Cu	Photothermal-enhanced CDT	4T1	12.3% (25 μg mL^{-1})	48
Cu-1	CDT/immunotherapy combined enhanced therapy	CT-26	1.45 ± 0.21	50

under white LED light irradiation, the generation of $^1O_2$ further increased the ROS level and resulted in a synergistic effect both *in vitro* and *in vivo*.

Apart from CDT-PDT combination therapy, Li *et al.* proposed nanoscale metalorganic particles (NMOPs) for the combination of PTT/CDT, which was prepared by the coordination-driven assembly of the carboxyl group of cyanine dyes with Cu (II) ions (**HA@Cy-Cu**).[48] In this system, cyanine was selected as a potential alternative organic PTT agent due to its inherent near-infrared absorption and high extinction coefficient; thus, Cu(II) could be reduced to Cu(I) by intracellular GSH and further catalysed H_2O_2 to generate toxic $^{\bullet}OH$ through a Fenton-like reaction, while hyaluronic acid (HA) was coated on the surface of the particles and acted as a tumor targeting unit. After being irradiated with 808 nm laser irradiation, the cell viability of COS-7, MCF-7, 4T1, and HeLa cells were significantly lower than that of organic PTT agent-treated cells. Thus, the combination of photothermal and CDT exhibited a more positive therapeutic outcome than single treatment. Besides, the Cu-based complex has also been employed in the CDT-involved trimodal synergistic treatment and/or immunotherapy.[49,50] Table 1 depicts the recent advances in Cu-based complex applied for enhanced CDT.

Conclusion and outlook

In summary, this review summarizes the latest advances in the elaborate design, rational construction, and purpose-oriented multifunctionalization of discrete copper-based complexes for enhanced CDT. The interactive characteristics of copper and ligands that contribute to the diversification of physical, chemical and physiological properties of copper complexes and make them potential alternatives/complements in CDT are taken into account. Although the application of metal complexes in CDT has achieved encouraging results, there are still several urgent issues and challenges remaining that should be solved.

(1) The complicated therapeutic mechanisms of CDT in the tumor microenvironment require further investigation as this will not only enhance the clarification of the metal center-mediated Fenton/Fenton-like reaction but also guide the rational design of efficient metal-based complex CDT agents.

(2) The organic ligand in novel multifunctional metal-based complexes with different physical and chemical properties should be purposefully selected and optimized, such as solubility, stability, targeting, toxicities, and charge regulation, endowing the systems with intrinsic kinetic features, biological activities and potential imaging-guided effective combination therapy with CDT.

(3) Increasing the concentration of H_2O_2 in the tumors has a positive effect on the production of hydroxyl radicals. It has been proved that composite functional nanomaterials can enhance the efficacy of CDT by endogenous stimulation or exogenous delivery to increase the level of H_2O_2 in the tumors. This approach, however, has not yet been explored in the design of metal-based complexes.

(4) To prevent the consumption of CDT agents during delivery, reduce side effects and achieve precise cancer treatment, it is necessary and urgent to develop tumor microenvironment stimuli-responsive intelligent drug delivery based on metal-based complexes. Endogenous stimuli mainly include acidic pH, glucose, GSH, and specific enzymes, while exogenous stimuli include light, heat, US and magnetic fields.

(5) Most importantly, residual metal ions after treatment remain a potential concern. Thus, theranostics unit should be urgently introduced into metal-based complexes to track the trajectory of CDT agents in the body and guide the structural design. Meanwhile, to better achieve the successful clinical transformation of CDT, it is necessary to conduct more safety evaluations (long-term safety and *in vivo* degradability) on the currently developed metal-based CDT agents.

Overall, numerous efforts have been made to optimize and expand the performance of metal-based complexes to enhance the CDT, but interdisciplinary cooperation is still needed to promote its development and clinical transformation. We firmly believe that the in-depth innovation and development of metal-based complexes, as well as subsequent optimization and improvement, will provide a promising choice for future tumor therapy.

Data availability

No additional data are available.

Conflicts of interest

There are no conflicts to declare.

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