


Research Progress on Improving the Efficiency of CDT by Exacerbating Tumor Acidification

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Abstract: In recent years, chemodynamic therapy (CDT) has received extensive attention as a novel means of cancer treatment. The CDT agents can exert Fenton and Fenton-like reactions in the acidic tumor microenvironment (TME), converting hydrogen peroxide (H₂O₂) into highly toxic hydroxyl radicals (\cdot OH). However, the pH of TME, as an essential factor in the Fenton reaction, does not catalyze the reaction effectively, hindering its efficiency, which poses a significant challenge for the future clinical application of CDT. Therefore, this paper reviews various strategies to enhance the antitumor properties of nanomaterials by modulating tumor acidity. Ultimately, the performance of CDT can be further improved by inducing strong oxidative stress to produce sufficient \cdot OH. In this paper, the various acidification pathways and proton pumps with potential acidification functions are mainly discussed, such as catalytic enzymes, exogenous acids, CAIX, MCT, NHE, NBCn1, etc. The problems, opportunities, and challenges of CDT in the cancer field are also discussed, thereby providing new insights for the design of nanomaterials and laying the foundation for their future clinical applications.

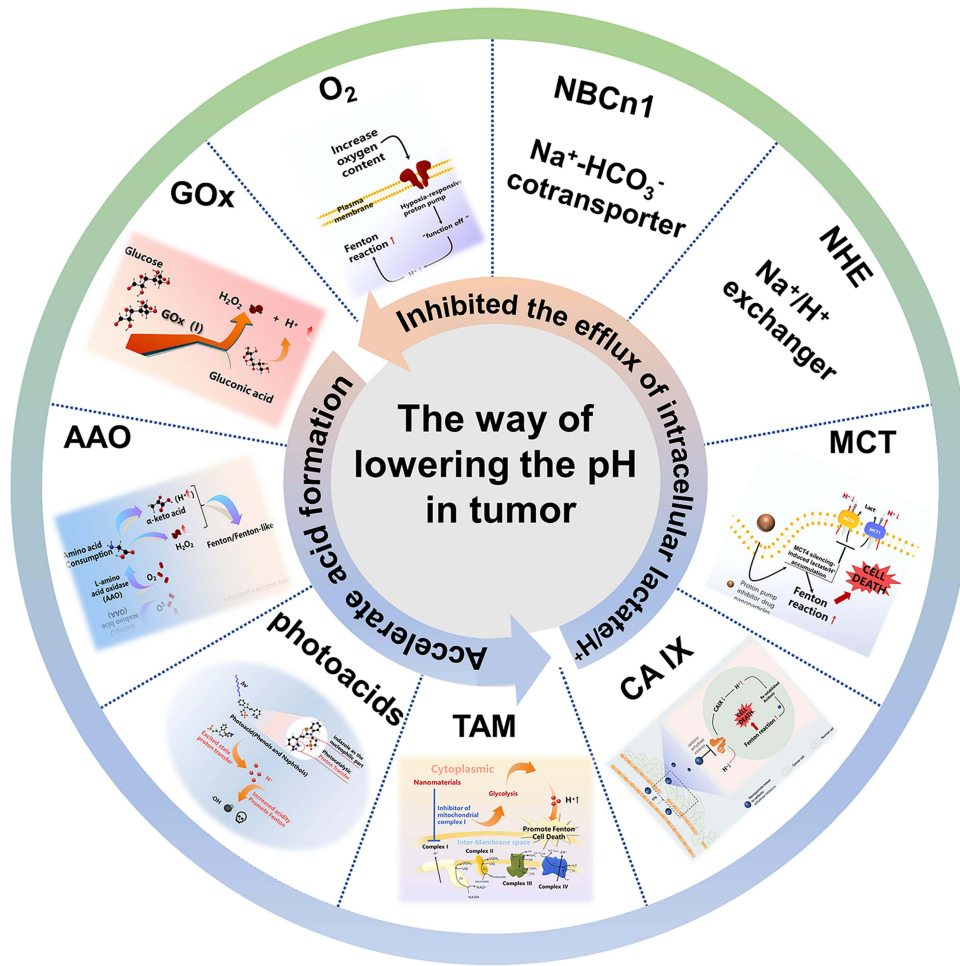
Keywords: chemodynamic therapy, Fenton/Fenton-like reactions, tumor microenvironment, reactive oxygen species

Introduction

Chemodynamic therapy (CDT) has been novel method in tumor treatment in recent years.^{1,2} CDT utilizes the characteristics of relatively low pH and high endogenous H₂O₂ in the tumor microenvironment (TME),³ and some transition metal ions, such as Fe²⁺, Mn²⁺, can act as catalysts to accelerate the Fenton-like reaction of H₂O₂ to produce the \cdot OH, which will kill tumor cells by oxidizing the lipids, nucleic acids, proteins and other biological molecules (Figure 1).⁴⁻⁸ Its excellent therapeutic effect on tumors has been verified in laboratory studies.⁹ Chemotherapy and radiotherapy, as treatments for cancer, have serious side effects, including toxicity and immunosuppression, which limit their anti-tumor efficacy and increase the risk of infection.^{10,11} Compared to them, CDT agents are less prone to serious side effects and drug resistance. Simultaneously, there is no need to be limited by oxygen and near-infrared light (NIR) as that of photothermal therapy (PTT) or photodynamic therapy (PDT). It can use the unique microenvironment in the tumor to produce oxidative stress reaction, realize the specificity and efficiency of tumor treatment, and reduce the damage to normal cells or tissues.¹² As a new way of cancer treatment, CDT can solve some drawbacks of traditional cancer therapy to a certain extent.

Although CDT has excellent prospects, there are still some challenges in the therapeutic effect of CDT agents.¹³ The main influencing factors are as follows. First, endogenous H₂O₂ (50–100 μ M) in tumor cells is difficult to support the continuous production of \cdot OH, which is insufficient to achieve numerous killing effects on tumor cells.^{14,15} Second, the concentration of glutathione (GSH) in normal cells is about 1–2 mM, but its concentration can reach 10 mM in cancer cells.^{16,17} So, a large amount of reduced GSH produced in TME will remove \cdot OH and reduce oxidative stress, resulting in the obstacles to CDT.^{18,19} CDT is highly dependent on Fenton reaction, which has high requirements for the biological microenvironment, a solid acidic with pH 2–4.²⁰ pH responsive nanoparticles can effectively release iron ions from

Graphical Abstract



nanocarriers to a certain extent in the acidic microenvironment of tumors with low pH.²¹ Subsequently, iron ions are effectively converted into highly active $\bullet\text{OH}$ by Fenton reaction for CDT. Whereas the extracellular pH (pHe) of TME is only about 6.8 and the intracellular (pHi) is approximately 7.2, which is higher than that of the Fenton reaction (pH 2–4).^{22–25} Therefore, due to the heterogeneity of tumor histopathology and physiology, it is expected to develop more active strategies of tissue microenvironment reprogramming through nanotechnology to improve the performance of CDT, which provides the compelling impetus for the Fenton reaction.²⁶

Increasing intracellular acidification is an effective way to enhance the Fenton reaction and efficacy of CDT. Tumor microenvironment reprogramming is essential for improving the responsiveness and performance of nanomedicines. Accelerating the formation of acid and inhibiting the efflux of intracellular lactate/ H^+ all can reduce the pH value of tumor. For instance, producing acid by enzyme catalysis, introducing photoacid in tumor, and production of H^+ by mitochondrial respiratory complex enzyme inhibitor, all can accelerate acid formation. According to inhibiting the efflux of intracellular lactate/ H^+ , pHe was indirectly reduced by inhibiting various proton pumps on the surface of the cell membrane and blocking the efflux of lactic acid. In this review, we focus on two perspectives to reduce intracellular pH, accelerating acid formation and inhibiting the efflux of intracellular lactate/ H^+ . We also discuss the inhibitors of different proton pumps, which provide a new perspective for the design of subsequent nanoparticles to realize the acidification function.

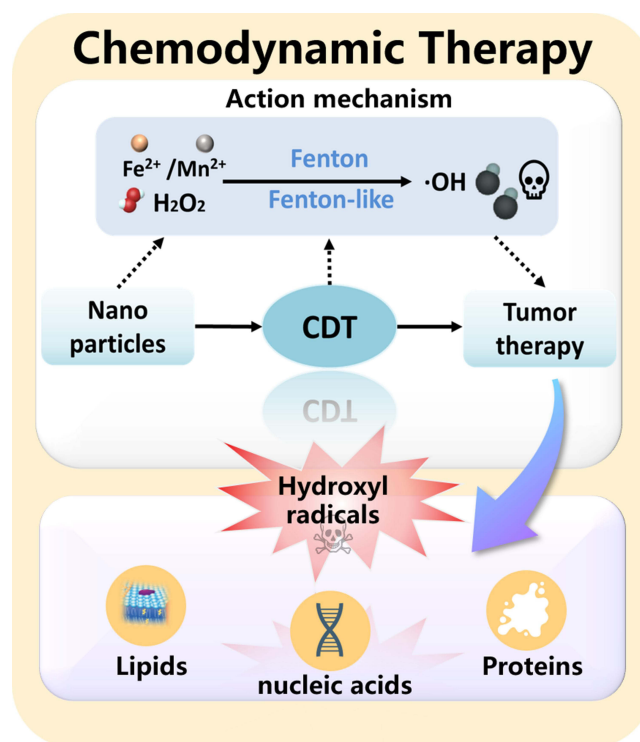


Figure 1 Schematic diagram of catalytic mechanism for cancer treatment of CDT.

Accelerate Acid Formation

Use of Catalytic Enzymes

A Low level of pH value is considered to be the critical factor for the efficacy of CDT in tumors.²⁷ It is believed that there are more glucose and amino acids in tumor tissue for its rapid proliferation, and gluconic acid and α -keto acid are their oxidation products, which are conducive to reducing pH value.^{28,29} The catalytic mechanism is shown in Figure 2.

GOx-Instructed pH Regulation

Glucose is an indispensable energy source in cells.³⁰ Compared with normal cells, rapid proliferating cancer cells will consume more glucose to produce more energy, so they are highly sensitive to changes in the level of glucose.^{31–33} Glucose in TME will convert to gluconic acid and H_2O_2 by introducing exogenous glucose oxidase (GOx), which is often used as one of the ways of tumor starvation therapy.^{34,35} Among them, gluconic acid can provide appropriate acidic conditions for the Fenton reaction. Similarly, acidification can also further decompose the nano-delivery system and promote the cascade reaction.³⁶ Thus, it is worth noting that the Fenton reaction induced by glucose acidification is a promising strategy of cancer therapy.

Glucose acid is widely considered as a promoter to improve Fenton reaction efficiency. A nanoscale Co-ferrocene metal-organic framework (Co-Fc NMOF) with high Fenton activity was synthesized by research group of Fang, and then combined with glucose oxidase (GOx) to construct a cascade enzymatic/Fenton catalytic platform (Co-Fc @GOx) for strengthening tumor treatment.³⁷ In this system, Co-Fc-NMOF acted as an effective carrier of GOx and could produce highly toxic $\cdot OH$ with a good Fenton effect. When this system reached the tumor microenvironment, GOx would catalyze the endogenous glucose to produce gluconic acid and H_2O_2 . Both the increase of intracellular acidity and H_2O_2 content in situ were conducive to the Fenton reaction of Co-Fc-NMOF, which would further promote the generation of ROS in the local tumor site. In 4T1 tumor-bearing mice, it was found that the tumor volume in the treated group was smaller than that in the control, showing the tumor inhibition by Co-Fc-NMOF introduced. It was noteworthy that the most significant antitumor effect could be obtained with Co-Fc

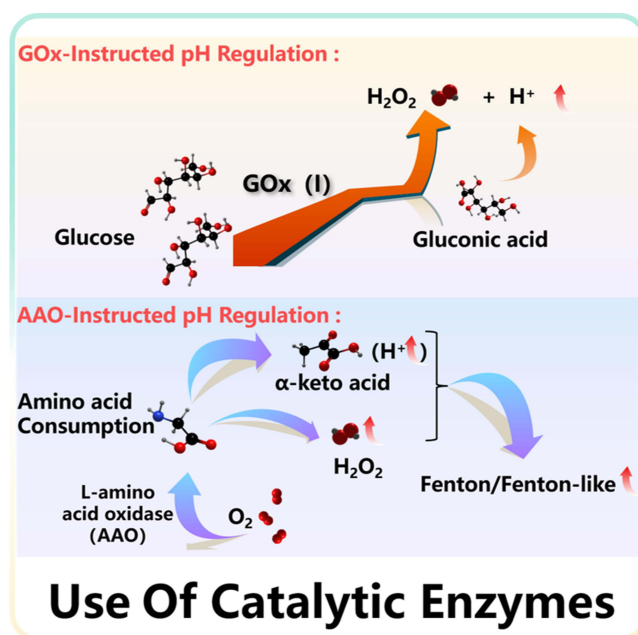


Figure 2 Mechanism diagram of promoting pH reduction by using of catalytic enzymes.

@GOx treated through the cascade enzyme/Fenton reaction. The authors also found that GOx alone had a limited inhibitory effect on tumor growth, which could be attributed to its diffusion and degradation in tumor tissues. Therefore, the appropriate nanocarriers were essential for the load and protection of GOx, which also could greatly avoid the damage of GOx to the normal tissues. Additionally, a kind of block copolymers was prepared by research group of Li, which was composed of poly(ethylene glycol) (PEG) and copolymerized monomers of camptothecin (CPT) and piperidine-modified methacrylate [P(CPTMA-co-PEMA)]. It could self-assemble into polymer vesicles in aqueous solution for encapsulation of GOx.³⁸ Vesicle structure had good integrity and stability in the process of intracellular action, so as to protect GOx from harsh environment and maintain long-term activity.^{39,40} Therefore, it was concluded that GOx could provide a potential therapeutic platform for tumor collaborative therapy and effectively regulate the tumor microenvironment.

The efficiency of GOx catalytic reaction is strongly dependent on oxygen concentration, but the hypoxia condition in TME leads to low activity of GOx.⁴¹ In order to overcome this problem, a dual-catalytic nanoreactor with oxygen-containing support was prepared by research group of Zhang. Hollow mesoporous silica nanoparticles (HMSNs) were used to load Fe₃O₄ nanoparticles as the Fenton reaction catalyst and GOx as the glucose oxidation catalyst on the HMSN surface. The oxygen-carrying perfluorohexane (PFC), acting as an oxygen carrier, was encapsulated in the pores of HMSNs. Finally, the cancer cell membrane was coated on the nanoreactor to construct the final GOx-Fe₃O₄-HMSNs-PFC/O₂@C. The results showed that GOx effectively consumed glucose in tumor and increased the generation of H₂O₂, which was further reacted with Fe₃O₄. Based on this, the Fenton reaction was enhanced and led to the increased production of highly toxic ·OH and the apoptosis of cancer cells in the end. For the hypoxia in the tumor microenvironment, PFC, containing an extensive amount of O₂, could improve the catalytic efficiency of GOx, increase the production of glucuronic acid and H₂O₂, and provide a suitable condition for the activation of CDT by Fenton reaction in the next step. In addition, treated with GOx-Fe₃O₄-HMSNs-PFC/O₂@C obtained higher tumor inhibition effect compared with other treatment groups in vivo. Take the life span of mice for example, the mice treated with Fe₃O₄-HMSNs-PFC/O₂@C was survived only for 13 days, greatly reduced about 17 days of that in control. These results might be attributed to the synergistic inhibitory effect of Fe₃O₄ nanoparticles, GOx, and O₂ against tumor, as well as the significant efficacy of GOx in Fenton-mediated CDT.¹³

In situ decomposition of H₂O₂ into O₂ in tumor cells by catalase-active nanozymes is also an important strategy for reoxygenation.³⁵ A multi-functional nanoreactor Fe-MIL-88B-NH₂@PFC-1-GOx (MPG), based on MOFs (Fe-MIL

-88B-NH₂), hydrogen-bonded organic frameworks (PFC-1), and GOx, was reported by Hu. Here, the function of GOx was like the previous report.⁴² Thanks to its excellent catalase-like (CAT) activity, O₂ was generated for the reaction of MPG with H₂O₂, which could alleviate the hypoxia in TME, further accelerate the glucose oxidation process, and improve the efficiency of CDT.¹⁵

It has been proved that gluconic acid can not only provide an appropriate pH for the Fenton reaction but also promote the decomposition and release of the acid sensitive nano-delivery system. The mesoporous iron oxide nanoparticles (IONP) were firstly modified by GOx, and then the artemisinin (ART) was loaded to design a cascade catalytic nanoplatfrom IONP-GOx@ART. Glucose oxidation was catalyzed by GOx and gluconic acid and H₂O₂ were produced, resulted in the tumor starvation and the activity of IONP-mediated Fenton reaction. The more acidic TME based on the gluconic acid generated was helpful for the release of Fe²⁺ and Fe³⁺ ions, which could generate ·OH through the Fenton reaction. In addition, the presence of Fe²⁺ would lead to destroy of the endoperoxide bridge in ART molecule, which caused the high level of ROS. All of the above results were benefit to CDT. This effect was again proved in 4T1 tumor-bearing mice, the tumor growth of treated by IONP-GOx@ART was significantly inhibited compared with that of IONP@ART,⁴³ demonstrating the great potential of GOx in anti-tumor therapy.

In short, GOx has been widely used in CDT, which provides a bright prospect for the anti-tumor treatment of CDT. The unique chemical reaction of GOx in tumor and its diversified applications make it a priority to regulate the acidic microenvironment of tumor. GOx can produce gluconic acid and abundant H₂O₂, which provides sufficient reactants for the Fenton reaction. So, GOx can regulate TME and provide a new idea for the treatment of malignant tumors. However, free GOx tends to overflow before reaching the tumor site and get the nonspecific accumulation in normal tissues, which inevitably limited the efficiency of CDT and enhanced its cytotoxicity. Therefore, the selection of nanocarriers is very important, which can be supported by MOF, mesoporous silica, or modified by chemical bonds. Since the catalytic reaction of GOx only works in the presence of O₂, it is imperative to provide sufficient O₂ to alleviate the hypoxic environment of the tumor, as well as to improve the catalytic efficiency of GOx.

L-Amino Acid Oxidase-Instructed pH Regulation

Amino acid (AA), a monomer for protein synthesis, is an important nutrient for the proliferation of cells, and it is also necessary for the survival of cells.^{44,45} In addition, AA is also an essential substance in the biosynthesis of lipids, nucleotides, and other substances. Therefore, the proliferation of tumor cells needs more AAs in response to meet the needs of the increased cell anabolism and rapid growth.⁴⁶ However, L-amino acid oxidase (AAO) can catalyze the oxidation of amino acids to produce α -keto acids, releasing hydrogen peroxide and ammonia.⁴⁷ Among them, α -keto acid is helpful to adjust the pH value of tumor and promote Fenton or Fenton-like reaction, and H₂O₂ can also continuously provide the substrates for Fenton reaction.

Research groups of Chu grafted L-Amino acid oxidase (AAO) on the surface of the hollow Fe³⁺/tannic acid nano capsules (HFe-TA), and covered 4T1 cancer cell membrane to form M@AAO@HFe-TA. In this system, AAO significantly consumed amino acids after entering cancer cells and produced α -keto acids and H₂O₂ to promote the formation of ·OH in HFe-TA. The cancer cell membrane on the surface of nanocapsules played a protective role in preventing AAO exposure and its potential cytotoxicity. Meanwhile, nanoparticles with certain immune escape and tumor targeting abilities could be got by the surface modification with the cancer cell membrane. Hence, this study might provide a new method to treat tumors and improve its biosafety and efficiency.⁴⁸

Photoacid-Instructed pH Regulation

Photoacid can produce H⁺ and reduce pH value under light stimulation.⁴⁹ Most of photoacid are the aromatic organic molecules and the weak acid in the ground electronic state. While in the first excited electronic state, they will generate a larger order of magnitude of H⁺.⁵⁰ The irradiated photoacid is expected to realize the remote space and time control of proton dissociation, and also realize the conversion of light energy into other types of energy.⁵¹ It has been confirmed that some phenolic derivatives, such as phenols and naphthols, can significantly increase acidity under light irradiation.⁵² At present, photoacid has been used as part of nanomaterials to improve the efficiency of CDT (Figure 3).

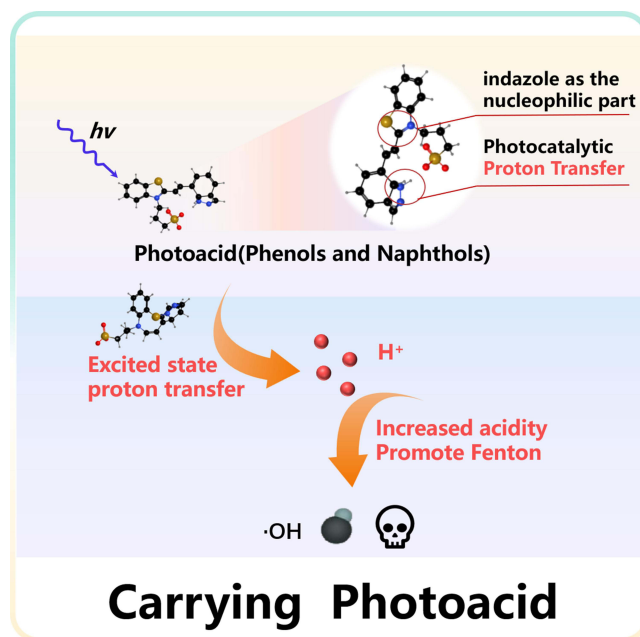


Figure 3 Mechanism diagram of promoting pH reduction by carrying photoacid.

Research groups of Chen designed a near infrared light (NIR)-controlled nano-proton supplier, whose upconversion nanoparticles (UCNPs) were used as the core of the MIL-88B coating for internal photoacids (PA) loading (UCNP @ MIL-88B @ PA, abbreviated as UMP). It was verified that the emission light of UCNPs under 980 nm laser irradiation could activate PA molecules cyclization to release H^+ . When UMP penetrated the cytoplasm of tumor cells, rapid dissociation of protons led to the decrease of the intracellular pH value. Under increasingly strong acidic conditions, the catalytic active sites Fe in the MIL-88B shell could effectively react with H_2O_2 to enhance the therapeutic effect of CDT on tumors. Therefore, all reliable evidence shows that PA can release H^+ under the control of light and play an effective role in CDT.⁵³

In summary, PA can specifically increase the H^+ concentration in TME under the control of specific light, but have almost no effect on the normal cells, with good biocompatibility. Therefore, the introduction of PA can significantly enhance the efficiency of Fenton/Fenton-like reactions and tumor treatment.

Inhibitor of Mitochondrial Complex I-Instructioned pH Regulation

Mitochondrial respiration is the basis of normal metabolism in most mammalian cells, which provides a central mechanism for coupling fuel and oxygen consumption with ATP synthesis.⁵⁴ According to previous studies, mitochondrial dysfunction will affect tumorigenesis.⁵⁵ Mitochondrial complex I, is called a reduced nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase (Q reductase), which can catalyze the NADH oxidation in the electron transport chain.⁵⁶ Complex I has a great impact on cell respiration and metabolic reprogramming and oxidative stress in a variety of malignant tumors (Figure 4). However, inhibitors of mitochondria complex I can reduce the mitochondrial respiration and ATP production, and promote cancer cells to adopt glycolysis resulting in higher lactate levels.⁵⁷ Therefore, complex I inhibitors are important in oncology research.⁵⁸

The research group of Shi developed a nanoplatfrom (FePt@FeOx@TAM-PEG) that could achieve efficient and specific anti-cancer effect through a dual pathway of cyclic amplification strategy. Tamoxifen (TAM), an inhibitor of mitochondrial complex I, could enhance glycolysis and lactate content, leading to the intracellular H^+ accumulation and overcoming the limitation of TME. Owing to the continuous cyclic release process, more FePt@FeOx were activated via a dual pathway of positive feedback loop, which would induce the strong ROS accumulation within cancer cells and lead to the significant increase of oxidative stress and apoptosis. Notably, the pH-responsive characteristics of TAM allowed

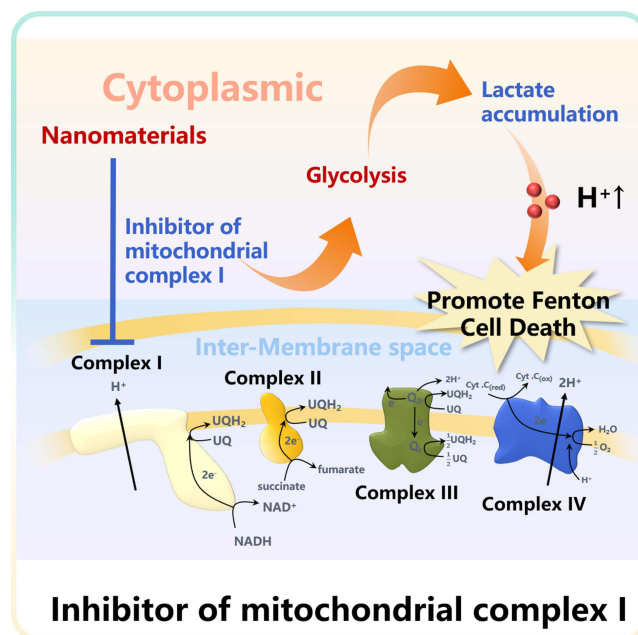


Figure 4 Mechanism diagram of promoting pH reduction by Inhibitor of mitochondrial complex I.

the FePt@FeOx to be “turn on” in acidic TME, but keep “turn off” under neutral conditions. Therefore, it is of great significance to further strengthen tumor therapy by reprogramming TME.⁵⁹

Inhibitors of mitochondrial complex I play an essential role in enhancing the effect of CDT. So, it is crucial to find new inhibitors of mitochondrial complex I. The research group of Ju confirmed that the anti-cancer drug carboxyamido-triazole (CAI) could inhibit mitochondrial respiration in cancer cells and enhance its anti-cancer activity by further regulating energy metabolism. When it was incubated with cancer cells, it could stimulate glucose uptake and lactate production, and inhibit oxidative phosphorylation (OXPHOS) in cancer cells, resulting in a decrease in the activity of the respiratory chain complex I. This result could lead to the lack of ATP production in mitochondria and force tumor cells to up-regulate glycolysis, leading to the increase of lactic acid.⁶⁰ In addition, META-IOD-BENZYLGUANIDINE (MIBG) could also inhibit the complex I of the mitochondrial respiratory chain. Related experiments showed that a progressive increase of the lactate was observed after incubation of the cells with glucose and rising concentration of MIBG.⁶¹

In conclusion, TAM, CAI and MIBG can influence mitochondrial respiration, up-regulate glycolysis and increase lactic acid content. Thus, they are expected to combine with CDT to efficiently treat cancer.

Inhibited the Efflux of Intracellular Lactate/H⁺

The acidic microenvironment is an important condition for promoting treatment of CDT.⁶² At present, the main proton pumps and proteins involved in tumor pH regulation are carbonic anhydrase IX (CAIX),⁶³ monocarboxylate transporters (MCT),⁶⁴ Na⁺/H⁺ exchanger (NHE),⁶⁵ Na⁺-HCO₃⁻ cotransporter (NBCn1) and so on,⁶⁶ and its regulation mechanism is showed in Figure 5. These inhibitors can regulate the activity of these proton pumps and proteins to inhibit the efflux of intracellular lactate/H⁺ and acidify the TME, which is more conducive to the occurrence of Fenton reaction. So far, some proton pumps and protein inhibitors have been widely reported and achieve the excellent therapeutic effects in inhibiting H⁺ efflux (Table 1).

CA IX-Instructioned pH Regulation

Carbonic anhydrase is widely distributed in mammalian cells, mainly in the cytoplasm (CA I, CA II, CA III, CA VII and CA XIII), mitochondria (CA VA and CA VB), membrane (CA IV, CA IX, CA XII, CA XIV and CA XV). Some carbonic anhydrase isoenzymes (CA II, CA IX and CA XII) are closely related to tumorigenesis, especially CA IX.¹¹⁰ Carbonic anhydrase IX (CAIX) is a zinc-containing transmembrane metalloenzyme. Carbon dioxide is also a key source of acid in

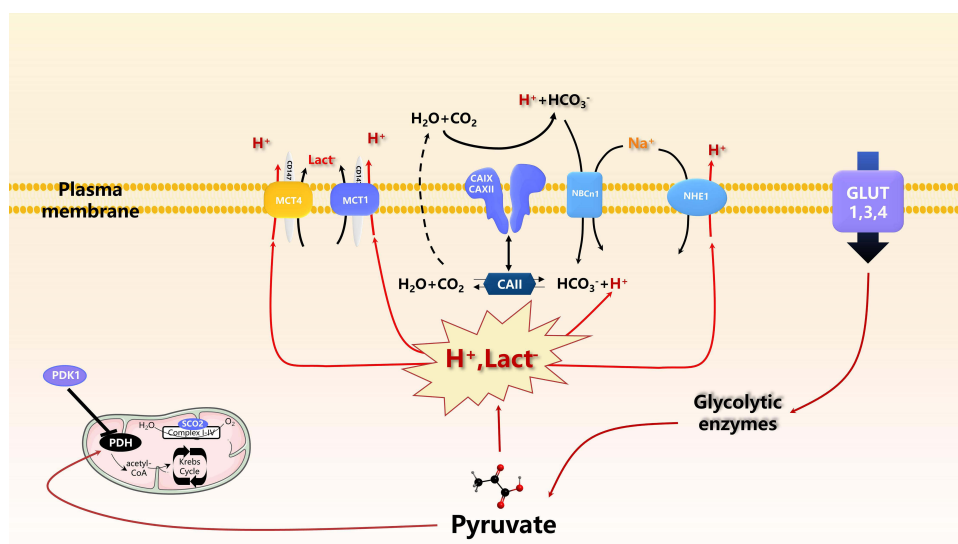


Figure 5 Mechanism of H^+ transport by various proton pumps.

tumors. CAIX can catalyze the conversion of CO_2 into bicarbonate and H^+ ($CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$), which will stabilize intracellular pH value and enhance the extracellular matrix decomposition and cell invasion.^{111,112} The structure of carbonic anhydrase has been widely studied. For instance, the CA IX protein (called MN or G250) detected in HeLa cells, contains an N-terminal proteoglycan-like domain, a CA domain, a transmembrane anchor, and a C-terminal cytoplasmic tail.¹¹³ It is upregulated in tumor cells under hypoxic conditions. The accumulation of hypoxia-inducible factor-1 α induces the expression of CAIX and causes a variety of downstream effects, including acidification of the extracellular, loss of cellular adhesion, and increased tumor cell migration.¹¹⁴ Therefore, CA IX has been recognized as a valuable target for cancer diagnosis and treatment because of its unique property in hypoxic TME.¹¹⁵

Fortunately, these special physiological processes can be reverted by inhibiting the activity of the CA IX enzyme through carbonic anhydrase IX inhibitor (CAI). Chen proposed a self-enhanced CDT to inhibit tumor occurrence and metastasis by constructing a tumor acidosis model AFeNPs@CAI. AFeNPs@CAI nanocomposites were composed of unique amorphous iron nanoparticles (AFeNPs) loaded with CAI, which facilitated the Fenton reaction and enlarged the oxidative damage to cells (Figure 6). At the same time, the over-expression of CAIX in cancer cells was inhibited by CAI, and the possibility of tumor invasion and metastasis was effectively inhibited by re-established tumor acidosis. The decrease of pHi effectively increased productivity of $\cdot OH$ by the Fenton reaction based on AFeNPs, and aggravated the oxidative stress in tumor cells and induced cells apoptosis.¹¹⁶ Thus, CAI not only potentiates the application of CDT in tumor therapy, but also provides a new anticancer idea of re-establishing TME for a better therapeutic effect, showing promising effective treatment of tumors.

In addition, research group of Angeli evaluated a series of telluride-containing compounds bearing the benzenesulfonamide group in vitro and found they could act as an effective inhibitor of carbonic anhydrase IX. These compounds exhibited inhibitory activity against tumor-associated CA IX at low concentrations (KI 2.2–2.9 nM), providing the possibility of treating the MDA-MB-231 breast cancer. In this case, the organotellurium derivatives as CAI inhibitors have opened up new avenues for novel antitumor agents.⁷⁴

Furthermore, it was found that the loss of CAIX expression in 4T1 mouse metastatic breast cancer cells mediated by shRNA led to the regression in orthotopic mammary tumors and inhibited spontaneous lung metastasis. Meanwhile, the stable depletion of CAIX in MDA-MB-231 human breast cancer xenografts also resulted in the weakening of primary tumor growth. What's more, a novel CAIX-specific small molecule inhibitor was used to treat CAIX-positive 4T1 breast tumors in mice. The inhibitor mimicked the effect of CAIX deficiency in vitro and significantly inhibited the tumor growth and metastasis in both spontaneous and experimental metastasis models but had no inhibitory effect on CAIX-negative tumors. The similar inhibitory effects were observed on primary tumor growth in orthotopic tumor mice bearing

Table 1 The Inhibitors for Proton Pumps

Proton Pumps		Inhibitors	Inhibition Model	Ref.
CAIX		Sulfonamide/sulfamate U-140 [sulfonamide] FC9-398A [ureidosulfamates] Glycosyl coumarin Indanesulfonamide shRNA siRNA Telluride containing compounds bearing the benzenesulfonamide Sulfonamide dicarbaboranes Saccharide-modified thiaziazole sulfonamide derivatives OCT [octyl disulfamate] 2H-benzo [e] [1,2,4] thiadiazin-3(4H)-one-1,1-dioxides (BTD) SLC-149[4-(3-(2,4-difluorophenyl)-oxoimidazolidin-1-yl) benzenesulfonamide] Saccharin/isoxazole and saccharin/isoxazoline hybrids Oxathiino[6,5-b] pyridine 2,2-dioxides 2,4-dihydro-1,2,4-triazole-3-thione derivative 9c	Breast tumor cell lines 4T1 tumor /MDA-MB-231 TNBC HT-29 cells HT-29 colorectal carcinoma cells 4T1 breast tumors BT-549 cell MDA-MB-231 cell - HT-29 MDA-MB-231 cell HCT-116 MDA-MB-231 cell MCF-7 cell MCF-7 cell A-498 kidney carcinoma cells	[67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82]
MCT	MCT1 MCT1/2 MCT4	α -cyano-4-hydroxycinnamate (CHC) AZD3965 AR-C155858 siRNA 2-Methoxy-4-N, N-dialkyl cyanocinnamic acids Diclofenac [F-18] FACH	Myeloma Human lymphoma and colon carcinoma cells 4T1 breast tumor cells PC3 tumor MDA-MB-231 xenograft tumor Melanoma -	[83] [84] [85] [86] [87] [88] [89]
NHE		Anti NHE1 siRNA Amiloride 5-(N-ethyl-N-isopropyl) amiloride Cariporide Cariporide [HOE-642] siRNA KR-33028 [4-cyano (benzo[b]thiophene-2-carbonyl) guanidine HMA [5- (N, N-hexamethylene)-amiloride] DMA [5- (N, N-Dimethyl) amiloride] Zoniporide Sabiporide DEPC (diethyl pyrocarbonate) KR-32570[5-(2-methoxy-5-chloro-5-phenyl) furan-2-yl-carbonyl] guanidine T-162559 SL-59.1227[imidazolypiperidine] EIPA [5-(N-ethyl-N-isopropyl) amiloride]	Hepatocellular carcinoma SMMC-7721 cell HepG2 cells MDA-MB-231 Mouse glioms Mouse glioms Triple-negative breast cancer MCF-7 spheroids Fibroblasts Vascular smooth muscle cell Fibroblasts H9C2 cells CHO-K1 cells Hamster fibroblast cell lines Human myeloid K562 cells	[90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104]
Na ⁺ -HCO ₃ ⁻ cotransporter NBCn1		shRNA HOE 694 plus DIDS SITS S0859(N- cyanosulphonamide compound)	MCF-7 spheroids OEC-M cells Human neutrophils HEK cell Glia-like progenitor cells	[105] [106] [107] [108] [109]

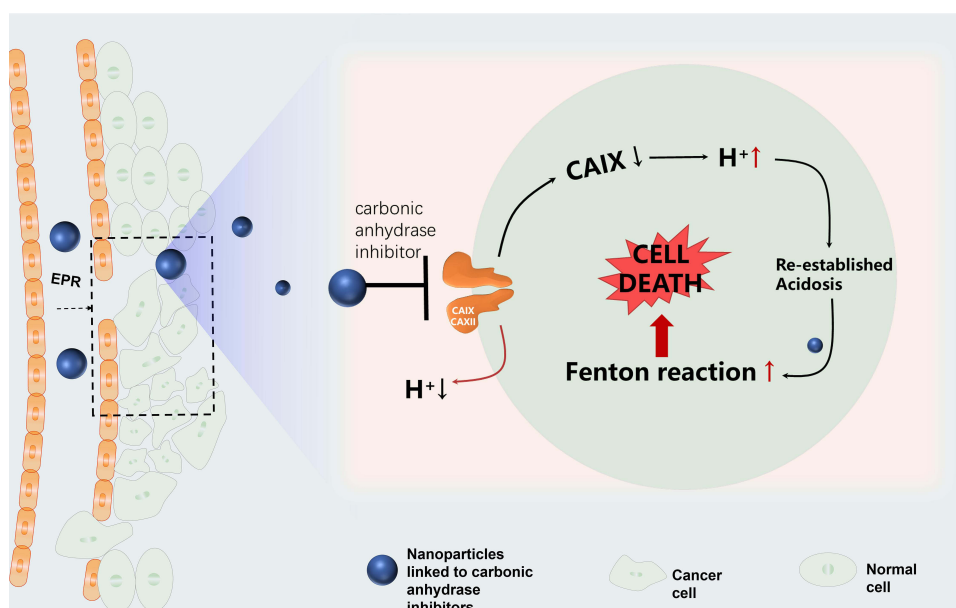


Figure 6 Schematic diagram of self-enhanced CDT via CAI.

lung metastatic MDA-MB-231 LM2-4Luc cells.⁶⁸ Therefore, targeting CAIX activity with specific drug inhibitors may help inhibit disease progression.

Some carbonic anhydrase-related proteins also affect the expression of carbonic anhydrase. Cullin-associated NEDD8-dissociation protein 1 (CAND1), a nuclear protein involved in gene transcription and SCF ubiquitin ligase complex assembly, which could interact with CAIX. In fact, this interaction was identified, and the low levels of CA IX were observed in cells with reduced CAND1 expression through shRNA-mediated interference. Due to the role of CAND1 in stabilizing CAIX, these molecules might have potent to reduce the amount of CAIX in hypoxic cancer cells. It might be a new prospect for the design of anticancer drugs targeting CAIX.¹¹⁷ In summary, the combination of CAI and CDT can significantly amplify the oxidative stress in tumor sites, effectively kill the tumor, as well as reduce its side effects on the normal tissues.

Monocarboxylate Transporters (MCT)

The Monocarboxylate transporters (MCTs), are a family of 14 members and products of the SLC16 gene family, among which MCT1–4 can transport one monocarboxylic acid molecule across the cell membrane such as L-lactate and pyruvate and so on.¹¹⁸ Different from other MCTs, MCT4 is activated by HIF-1 α and will exhibit 3–5 fold mRNA expression during hypoxia, showing significantly higher tissue expression in hypoxic region of tumor site.^{119,120} MCT-4 is also a low-affinity and high-capacity lactate transporter, which exists in cells with increased glycolytic activity and participates in the release of lactate in cell glycolysis.¹²¹ MCT4 is highly expressed in various types of solid tumors, for instance, the breast cancer.¹²² Previous studies showed that the cells expressing MCT-4 showed stronger invasion behavior than those without MCT-4 expression.¹²³ Therefore, silencing MCT-4 gene and using MCT4 inhibitors are expected to reduce pHi and improve the efficiency of CDT.

An innovative amorphous iron oxide (AIO) RNAi NP platform was constructed by research group of Liu. RNAi NP platform could regulate the glycolysis pathway by silencing MCT-4 to block the outflow of intracellular lactate/H⁺, optimizing the catalytic efficiency of Fenton/Fenton-like reactions and upgrading the therapeutic performance of CDT. It was worth noting that blocking intracellular lactate efflux by MCT-4 silencing also could further stimulate more H₂O₂ production to amplify the Fenton-like reaction and oxidative damage to tumor cells, and result in the effective combination therapy (Figure 7).⁸⁶ In short, MCT-4 inhibitors are of great significance for the upregulation of total ROS by CDT, which ultimately improves the anti-cancer efficiency of CDT.

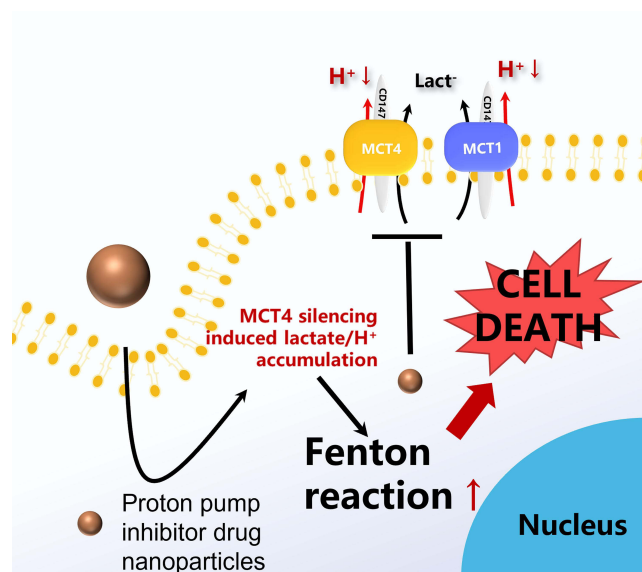


Figure 7 Anticancer mechanism of MCT 4.

Na⁺/H⁺ Exchanger (NHE1)

NHE1, an H⁺-regulated membranous transport protein, is encoded by human solute carrier family 9A1 (SLC9A1) gene and can maintain an acidic extracellular pH in cancer cells.^{65,94} NHE1 drives H⁺ efflux to exchange Na⁺ influx to maintain pHi, which is an important driving force for glycolytic metabolism.¹²⁴ The transmembrane domain of NHE1 is necessary for ion transport, and its ~300-residue long, regulatory C-terminal cytosolic tail controls the pHi set point of the transporter and is also required for allosteric NHE1 regulation.¹²⁵ So far, 10 isoforms have been identified in the human NHE family.¹²⁶ In addition, the hypoxic and serum-depleted tumor microenvironment further promote excessive activation of NHE1.¹²⁷ Researches show that the activation of NHE1 enhances the migratory capability and invasiveness of human melanoma cells and breast carcinoma cells.¹²⁸ Thus, it is important for inhibiting H⁺ efflux by choosing a specific NHE1 inhibitor.

NHE1 inhibitors partially inhibit NHE1 by competing with Na⁺ at the transport site.¹²⁹ At present, NHE1 inhibitor has not yet been combined with CDT, but their advantages in tumor treatment have been proved. The stable shRNA-mediated NHE1 gene knockdown (KD) in the MDA-MB-231 triple-negative breast cancer (TNBC) cell line significantly lowered pH(i) and capacity for pH(i) recovery after an acid load.¹³⁰ KR-33028 (4-cyano (benzo[b]thiophene-2-carbonyl) guanidine), an effective and selective NHE1 inhibitor, could inhibit metastatic of TNBC cells and reduce cell invasion through the extracellular matrix. Meanwhile, the effect of KR-33028 on MDA-MB-231 cells lacking NHE1 expression (231koNHE1) was also evaluated. It was found that there was no difference between untreated control cells and 231koNHE1 cells treated with KR-33028. Thus, KR-33028-mediated inhibition of NHE1 has implications for limiting cell metastasis in vivo.⁹⁶

The three-dimensional (3D) spheroids with MDA-MB-231 and MCF-7 cell were constructed and treated with pyrazinoylguanidine-type NHE1 inhibitors for 2–7 days, followed by analyses of the viability and death-associated signaling. It was found that this type of NHE1 inhibitor could reduce the viability of breast cancer spheres in a dose-dependent manner.⁹⁷ In conclusion, the introduction of NHE1 inhibitor in the nanoparticle is helpful to prevent H⁺ efflux and effectively prevents the invasion of the TNBC. Therefore, by inhibiting NHE1 activity not only contributes to CDT optimization, but also provides an opportunity to develop more specific approaches to regulate pH of the TME.

Na⁺-HCO₃⁻ Cotransporter NBCn1

Na⁺-HCO₃⁻ cotransporter NBCn1 constitutes the majority of the acid extrusion capacity in human breast carcinomas.¹³¹ Most evidence indicates that the protein expression of cotransporter NBCn1 is increased in primary breast carcinomas

and lymph node metastases. Compared to the matched normal breast tissue, the expression of NBCn1 protein in human breast cancer is about twofold to threefold of that in normal one.¹³² Driven by the Na^+ concentration gradient, NBCn1 normally can move Na^+ and HCO_3^- into cells.¹³³ The upregulated cellular net acid extrusion in breast cancer depends on NBCn1-mediated HCO_3^- uptake.^{130,134} However, Na^+ - HCO_3^- cotransporter NBCn1 inhibitor can block HCO_3^- uptake and its transformation to carbon dioxide driven by CAIX, and finally inhibiting H^+ emission, maintaining pH values in cell, and thereby limiting cell proliferation and breast cancer occurrence. Thus, NBCn1 is widely expressed and likely to play an important physiological role in pHi regulation in numerous tumors.¹³⁵

The functional consequences of NBCn1 knockout (KO) were tested during the breast cancer development. The results showed that NBCn1 gene mutation delayed the development of breast cancer. Compared with wild-type (WT) mice, the tumor growth rate was about 65% decreased in NBCn1 KO mice, while the incubation period of breast tumors was prolonged. The cell proliferation rate of NBCn1KO cancer mice was about 60% lower than that of WT by Ki-67 and phosphohistone H-3 staining. It was also found that CO_2 , HCO_3^- dependent net acid extrusion was suppressed and the steady-state pHi decreased in breast cancer tissue of NBCn1 KO mice.¹³⁶ The disruption of NBCn1 expression also delayed the growth of the ErbB2-induced breast carcinogenesis. Take the survival period for example, it was about 9.5 months for a median tumor-free in wild-type mice, but prolonged to 12 months in NBCn1-knockout mice.¹³⁷ Thus, these findings demonstrated that NBCn1 might act as a target for anti-cancer therapy, even combined with CDT to improve the efficiency of cancer treatment.

Conclusion

Compared with traditional cancer therapy, CDT is a new cancer treatment method.¹³⁸ Because of its high specificity and sensitivity, researchers have paid extensive attention to converting H_2O_2 into highly toxic $\cdot\text{OH}$ by initiating Fenton and Fenton-like reactions.¹³⁹ Although the TME is weakly acidic, its pH value is unsuitable for Fenton reaction occurrence.¹⁴⁰

In order to overcome the limitation, strategies to improve CDT efficiency in view of acidification is summarized in this review. Increasing the concentration of H^+ in tumor cells is the first way to be studied. For example, by introducing the catalytic enzymes and exogenous acids, such as GOx, AAO, PA, is able to reduce the pH value in tumors and improve the efficiency of CDT against cancer. The mitochondrial complex I inhibitor is used to block the oxidative phosphorylation of cell respiration, resulting in forcing cells to produce lactic acid by anaerobic glycolysis and increasing the intracellular acidity. Similarly, the proton pump protein inhibitors, such as CA IX, MCT-4, NHE1, NBCn1, are introduced to inhibit intracellular lactate/ H^+ efflux and reduce intracellular pH. These catalytic enzymes and inhibitors will serve as potential cancer adjuvants for CDT. Except for NBCn1, other proton pumps are mainly activated under anoxic conditions. Therefore, we can also inhibit the function of proton pump from the perspective of increasing tumor oxygen concentration, so as to improve the acidity of TME and the efficiency of CDT.

Many research works have proved that acidification of TME does have effect in promoting the action of CDT, but there are still some challenges. For GOx, it is critical to ensure that its internal substance, GOx, is not released before reaching the tumor site. GOx catalysis can consume glucose and O_2 , which will damage the normal cells if the leakage occurs during transportation.¹⁴¹ Therefore, a variety of fine therapeutic nanocarriers were developed, including cell membrane (CM),^{142,143} metal polyphenol networks,¹⁴⁴ metal-organic frameworks,² zeolitic imidazolate framework.¹⁴⁵ All of these nanocarriers were confirmed to maximize its safety and improve the therapeutic effects and reduce side effects.

In addition, acidification can combine with other factors to affect Fenton reaction. Firstly, by strengthening the conversion rate of Fe^{3+} to Fe^{2+} , the Fe^{3+} local electron density can be adjusted to increase the electron density. At this time, electrons will move the atoms from the non-reaction center to the reaction area and the reaction dynamic process is accelerated.^{146,147} Secondly, regulating the TME to enhance CDT performance, such as increasing H_2O_2 concentration in tumor,^{148,149} and reducing the excessive intracellular antioxidant GSH,¹⁵⁰ can improve efficiency of CDT.¹⁵¹ In addition, CDT-based combination therapy can be developed, such as CDT-PDT,¹⁵² CDT-PTT,^{153,154} CDT-chemotherapy,¹⁵⁵ CDT-immunotherapy,¹⁵⁶ CDT-RT,¹⁵⁷ CDT-SDT,¹⁵⁸ CDT-starvation therapy,¹⁵⁹ which can produce significant synergistic effects and reduce the side effects of CDT agents. However, in order to address the current barriers of CDT for clinical applications, we should try to avoid large doses, complex synthesis processes and cumbersome auxiliary devices when

designing nanoplatfoms.¹⁶⁰ It is important to develop a simple and efficient CDT nanoplatfom for the field of cancer nanomedicine.

At present, different from the classic pH-dependent Fenton/Fenton-like reaction, some researchers have developed a pH-independent reaction to increasing the production of $\cdot\text{OH}$, which is also confirmed the certain potential in CDT treatment, but its mechanism is still needed to be explored.¹⁶¹

In summary, CDT shows a broad application prospect in cancer treatment and is worth further exploration in different tumors.¹⁶² The acidic TME is crucial for Fenton and Fenton-like reactions and plays a decisive role in the anti-tumor effect of CDT.¹⁶³ So, it is the unremitting goal to design nano-platfoms with simpleness, good biocompatibility, low toxic, and high efficiency to CDT, as well as the perspective therapy to achieve early clinical application.

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Disclosure

The authors report no conflicts of interest in this work.

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