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Chemodynamic Therapy: Tumour Microenvironment-Mediated Fenton and Fenton-like Reaction

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MINIREVIEW

Abstract: Tailored to the specific tumour microenvironment, which involves acidity and the overproduction of hydrogen peroxide, advanced nanotechnology has been introduced to generate the hydroxyl radical (•OH) primarily for tumour chemodynamic therapy (CDT) via the Fenton reaction and Fenton-like reaction. Numerous studies have investigated the enhancement of CDT efficiency, primarily the increase in the amount of •OH generated. Notably, various strategies based on the Fenton reaction have been employed to enhance •OH generation, including nanomaterials selection, modulation of the reaction environment and external energy fields stimulation, which are discussed systematically in this minireview. Furthermore, the potential challenges and the methods used to facilitate CDT effectiveness are also presented to support this cutting-edge research area.

1. Introduction

The Fenton reaction, which is simply defined as the generation of highly oxidative hydroxyl radicals (•OH) from hydrogen peroxide (H₂O₂), is catalysed by ferrous ion (Fe²⁺) and has been widely used to remove refractory organics.1-3 After extensive research, advanced nanotechnology has created a broad stage for the further development and extension of the Fenton reaction, such as iron-based nanomaterials for the Fenton reaction and Fenton-like reaction,4-6 other metal-based nanomaterials, and graphene oxide for the Fenton-like reaction.6 However, a major issue encountered by scientists is how to broaden the applications of the Fenton reaction and Fenton-like reaction, which would also provide possibilities and has prompted many studies in other fields in addition to the ecological environmental field. Characterized by mild acidity,7 H₂O₂ overproduction,8 low catalase activity9, and hypoxia,10 the tumour microenvironment (TME) not only provides a suitable environment and nutrition for tumour development11 and metastasis12,13 but also furnishes the "gate" for selective and efficient tumour treatments. In this case, numerous TME-responsive nanomaterials have been developed in recent decades, the majority of which are TME-responsive drug delivery nanocarriers4-8 that have deficiencies, such as insufficient drug loading and easy leakage to damage normal tissues. Moreover, studies focusing on current clinical treatments would provide researchers with effective guidance to explore more suitable new therapies. For example, radiotherapy generates reactive oxygen species (ROS)14 in the tumour area through X-rays to destroy the tumour. Certain chemotherapeutic drugs, such as tirapazamine (TPZ)15,16 and doxorubicin (DOX),17 also generate ROS to fight tumours. In addition, the drug artemisinin is a highly effective treatment for malaria. One of the principles underlying the effects of this drug is that the iron in the residual haeme observed in patients with malaria induces the decomposition of artemisinin by catalysing the formation of a peroxide bridge to produce hydroxyl radicals,18,19 which are highly active and lethal, subsequently eliminating the malaria parasite. Chemists quickly linked this mechanism to the classical Fenton reaction.

After considering these different fields, chemodynamic therapy (CDT), an emerging therapeutic strategy, was recently proposed by our group20 and defined as in situ treatments using the Fenton reaction or Fenton-like reaction to generate •OH in tumours. Briefly, iron-based nanomaterials dissolve ferrous ions under the mildly acidic conditions of the TME and initiate the Fenton reaction to overproduce H₂O₂, generating •OH to trigger apoptosis and inhibit the tumour. Most importantly, this approach ensures normal tissue safety in some degree, because the Fenton reaction is substantially suppressed under the slight alkaline conditions and in the presence of insufficient H₂O₂ in a normal microenvironment.21 Even so, the potential toxicities of nanomaterials should be taken into consideration for further applications. This strategy not only broadens the applications of the Fenton reaction but also simplifies its potential for clinical translation. Compared with chemotherapy, radiotherapy, photothermal therapy and photodynamic therapy, CDT has the following advantages: i) highly logical and selective, and ii) and activated by endogenous stimulus. Meanwhile, we could also find the connections between CDT and current following clinical cases except for the malaria treatment using artemisinin: The antitumor principle of bleomycin22,23 is that the bleomycin is firstly embedded in DNA, and then the complex of bleomycin with iron would generate superoxide and hydroxyl radicals to break DNA strand. At the same time, the cardiotoxicity of anthracycline drugs is mainly from the reactive oxygen species, especially hydroxyl radicals, generated by the binding iron ions with H₂O₂24 which also provides enlightenment for CDT. Therefore, studies aimed at the further development of CDT have flourished, which supports the potential utility of CDT for clinical translation.

Since the development of CDT, the selection of suitable materials, the modulation of the reaction environment (reduced pH levels, increased amounts of reactants and decreased amounts of glutathione) and the assistance of an exogenous energy field have been used to optimize the effect of CDT, which relies on the guidance of the Fenton or Fenton-like reactions and basic chemical principles. Although the majority of the existing CDT agents are iron-based inorganic nanomaterials, other inorganic nanomaterials and organic nanomaterials have also been used to enrich the library. Moreover, nanomaterials used for CDT without low pH dependence are also satisfactory choices. Nanomaterials have the ability to exclusively produce protons or H₂O₂ in tumours should also be taken into...
2. Nanomaterials selection

Due to the irreplaceable role of the catalyst in the Fenton reaction and Fenton-like reaction, the selection of nanomaterials (iron-based inorganic materials, other metal-based inorganic materials or metal-organic framework nanomaterials) is very important.

2.1. Iron-based inorganic nanomaterials

The first step in increasing the CDT efficiency is to increase the catalyst ion amount. The method should closely linked with the TME, such as the acidity level, which is created by the generation of large amounts of lactic acid resulting from the upregulation of glycolytic metabolism. For instance, our group synthesized amorphous FeO nanoparticles (AFeNPs) (Figure 1a), which were rapidly ionized in an acidic TME to release more Fe ions than Fe nanocrystals (FeNCs) for CDT, because it had the reactive nature of metallic glasses. As presented in Figure 1b and Figure 1c, the release rate of ferrous ions from the AFeNPs reached 57% at a pH of 6.5 and 100% at a pH of 5.4 within 6 h, which were much higher than those observed for the FeNCs. Moreover, both AFeNPs and FeNCs tended to slowly release ferrous ions at a neutral pH. These results confirmed the capacity of AFeNPs for selective ferrous ion release, thus ensuring the efficiency of CDT. In addition, many other iron-based nanomaterials, including Fe oxides, [30-32] FeOH, [33] and MnFe2O4, [34,35] have also been introduced as CDT agents, but none have focused on increasing the release of the catalytic Fe ions.

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2.2. Other metal-based inorganic nanomaterials

Although the TME exhibits the characteristics of a low pH and hydrogen peroxide overproduction, it also has a higher concentration of GSH than normal tissues, which consumes the generated hydroxyl radicals, thereby limiting the CDT effect. In addition to the catalytic effect of ferrous ions, other transition metal ions, including Mn²⁺, Ti³⁺, Cu²⁺ and Co²⁺ ions, could also act as catalytic ions. From this perspective, the combination of the GSH consumption with increasing catalyst ion generation in one nanomaterial is both a challenge and a potential application. For example, Lin et al. prepared a CDT agent, MnO₂-coated MS NPs (MS@MnO₂ NPs), which combined the ·OH generation and GSH depletion. As depicted in Figure 1d, the MnO₂ shell reacted with GSH to produce Mn²⁺ and glutathione disulphide (GSSG) and subsequently triggers ·OH generation from H₂O₂ in the presence of HCO₃⁻/CO₂. The efficiency of ·OH generation was investigated by monitoring methylene blue (MB) degradation. Compared with the group treated with H₂O₂ and MnCl₂ in aqueous solution, apparent degradation of MB was detected after a 30 min incubation in NaHCO₃/CO₂ buffer, which confirmed the indispensable role of HCO₃⁻/CO₂. In addition, MS@MnO₂ NPs still exhibited sufficient MB degradation in the presence of a high concentration of GSH of 10 mM (Figure 1f and 1g), which was approximately 1.3 times higher than the concentration of free Mn²⁺, suggesting that MS@MnO₂ NPs increased the efficiency of CDT. Therefore, the combination of other metal systems with the TME is a promising approach for improving CDT efficiency.

2.3. Metal-organic framework nanomaterials

In addition to inorganic nanomaterials, nanomaterials with a metal-organic framework (MOF) and macromolecular nanoparticles (the assembly of small molecules and does not have the periodic network structure) also have the potential to be utilized for CDT. Compared with stable inorganic nanomaterials, MOF and macromolecular nanomaterials have been designed for therapies or imaging because of their flexibility and better responsiveness. Zheng et al. synthesized a metal-organic network (MON)-p53 with a core-shell structure based on a MOF, and the resulting network resulted from the coordination between Fe³⁺ and tannic acid (Figure 2a). In the system, ferric ions generated ·OH, and the expression of p53

Figure 1. (a) Preparation of AFeNPs. (b and c) Time-dependent ion release from FeNPs and AFeNPs at different pH values. Reproduced with permission from ref. [25]. Copyright 2016, Wiley-VCH. (d) The mechanism underlying the effects of MnO₂ as an enhanced CDT agent for cancer. (e) UV/Vis absorption spectra and photo (inset) of methylene blue (MB) after degradation by the Mn²⁺-mediated Fenton-like reaction in different solutions. (f) MB degradation of different groups. (g) Bar graph showing the percentage of MB degradation in various groups. Reproduced with permission from ref. [38]. Copyright 2018, Wiley-VCH.

Figure 2. (a) Schematic illustrating the preparation of MON-p53. (b) Schematic illustrating MON-p53-mediated anticancer therapy. (c) Viability of HT1080 cells treated using different metal−organic networks coated with PEI/p53 and erastin with metal ions. (d) Curves showing HT1080 tumour volumes in mice during the first 25 days of treatment. Reproduced with permission from ref. [40]. Copyright 2016, American Chemical Society.
protein inhibited the expression of the SLC7A11 protein expression, thereby inducing GSH depletion to further enhance the ·OH yield (Figure 2b). Various metal ions (Fe²⁺, Fe³⁺, Al³⁺, Co²⁺, Ni²⁺, Cu²⁺, Mn²⁺ and Ca²⁺) had been introduced to evaluate the cytotoxicity towards HT1080 cells, and significant cytotoxicities were detected in cells co-incubated with MON-p53 and Fe²⁺ and Fe³⁺, confirming that the MON-p53-induced cell death was mediated by an iron-dependent mechanism (Figure 2c). Furthermore, the shell p53 protein exhibited the ability to regulate the SLC7A11 level and block GSH synthesis, which ultimately enhanced the CDT efficiency in vivo, as evidenced by the changes in the tumour volumes of different groups (Figure 2d). In addition, Burachaloo et al. fabricated a reduced iron MOF conjugated with folic acid (rMOF-FA) as the CDT agent (Figure 3a). The MOF was unstable in an acidic environment and rapidly released iron ions for CDT, while it was stable at neutral pH (Figure 3b). As shown in Figure 3c, the rMOF-FA released approximately 100% of the iron ions at pH 5.0 compared with the negligible release observed at neutral pH, consistent with the well responsiveness and specificity of amorphous iron nanomaterials. Other advantages of MOF, such as the high porosity and large surface area could also been utilized for promoting CDT efficiency.

3. Modulation of the reaction environment

The Fenton reaction is affected not only by the catalytic ions amount but also by the reaction environment, including the pH and the amount of hydrogen peroxide or GSH. Recently, several studies focused on modulating the reaction environment (reducing the pH, generating more H₂O₂ and decreasing the GSH amount) for CDT have emerged and presented potential applications, which promotes researchers to develop additional methods to optimize the treatment effect.

3.1. Reducing pH levels

For the Fenton reaction, the optimal reaction pH ranges from 2-4 because of the following reasons: i) it inhibits the precipitation of ferrous and iron ions in a low pH environment; and ii) in addition, hydrogen peroxide would be degraded under extremely low pH conditions. For tumours, the pH of the TME predominantly ranges from 6.5 to 7, the endosomes of tumour cells have a pH of approximately 5.0 and lysosomes have a pH of approximately 4.5. For most materials, the number of catalytic ions released is limited primarily by the requirement for a weakly acidic environment, and the Fenton reaction is also inhibited in a weakly acidic environment. Therefore, reducing the pH of TME or delivering the nanomaterials to the nucleus or lysosomes might also enhance the CDT efficiency.
Liu et al. developed an amorphous iron oxide (AIO) RNAi NP nanoplatform (Figure 4a). They encapsulated the siRNA within NPs to limit enzymatic contact, degradation and burst release during circulation in the blood, and the small size of the NPs permitted it to deeply penetrate tumour tissues. This novel strategy was summarized as an initial blockade of intracellular lactate/H⁺ production via MCT4 silencing to induce cell acidosis and the subsequent release of large amounts of iron ions to react with more H₂O₂ molecules, which was also stimulated by the intracellular lactate efflux block, as depicted in Figure 4b. As shown in Figure 4c, AIO NPs penetrated greater depths of the tumour than polymer NPs loaded with Cy5.5-siRNA, thus potentially extending the treatment area to enhance CDT efficiency. Moreover, the expression of MCT4 analysis by western blotting and immunofluorescence staining (Figure 4d and 4e) confirmed the silencing effect of AIO NPs. The intracellular H₂O₂ concentration was substantially increased after silencing in PC3 cells, which resulted from intracellular lactate accumulation (Figure 4f). Similarly, MCT4 expression was also inhibited, and the AIO NPs exhibited sufficient inhibition on tumour growth in vivo (Figure 4g).

3.2. Increasing the H₂O₂ level and decreasing the GSH level

The concentration of H₂O₂ in tumour cells is up to 100 µM, while it is just 20 nM in normal tissues. However, the amount in tumour cells is still low to serve as an efficient CDT. The strategy of inhibiting MCT4 expression using the (AIO) RNAi NP nanoplatform not only reduces the pH but also increases H₂O₂ generation. Additionally, Wang et al. also constructed integrated multifunctional polymeric nanoparticles for tumour therapy. The micelles had cores formed by L-ascorbyl palmitate (PA) and ferrocenecarboxylic acid hexadecyl ester (DFc) and poly(ethylene glycol) (PEG) shells, which were linked via the host-guest interaction. Responding to the pharmacological concentration of ascorbic acid, the nanoparticles promoted H₂O₂ generation, and the Fc groups subsequently suppressed tumour growth (Figure 5b). The hydroxyl radicals were then monitored by detecting the fluorescence intensity at a wavelength of 425 nm of 2-hydroxyterephthalic disodium, which was the product of the reaction between disodium terephthalate and hydroxyl radicals. Excitingly, Figure 5c showed the large increase in the fluorescence intensity of PA/Fe-micelles after 3 h compared with the nearly unchanged fluorescence intensity of PA and DFC alone, which confirmed the sufficient generation of -OH. Meanwhile, comet assays of different groups (Figure 5d) were conducted to reveal the degree of DNA damage, which also revealed the efficient treatment effect of PA/Fe-Micelles (Figure 5e). In addition to the use of MnO2,[38] the strategy of introducing RNA to modulate the amount of H₂O₂ production is also suitable for decreasing the amount of GSH.

Huo et al. fused natural glucose oxidase (GOD) with biodegradable dendritic mesoporous silica (DMS) nanoparticles and ultrasmall Fe₃O₄ nanoparticles into one system for tumour ablation. GOD served as the enzyme that reacted with glucose in the tumour area to generate H₂O₂ and DMS released Fe₃O₄ to initiate a Fenton-like reaction, generating amounts of -OH (Figure 6a). Furthermore, the anticancer ability of GDF NCs at the cellular level was evaluated using a calcine-AM/PI probe, and the confocal laser scanning microscope (CLSM) images showed well CDT effect on 4T1 cells (Figure 6b). The blood glucose levels decreased 30 min after the injection of the nanoplatform and recovered 1 h after the injection (Figure 6c), which indicated glucose consumption by GOD. Nevertheless, several issues remain to be resolved. First, the glucose consumption process also requires oxygen, but the TME is relatively hypoxic, which would inhibit the generation of H₂O₂. In addition, a lack of GOD targeting to the TME would also enable this enzyme to react with glucose in normal tissues, reducing the selectivity of the reaction.
4. Stimulation by external energy fields

Despite the limitations of external energy fields, such as an insufficient penetration depth of light and heat radiation in normal tissues, external energy fields (e.g., light, heat, ultrasound, magnetic fields and electric fields) are more feasible for development as auxiliary treatments to speed up Fenton reaction and Fenton-like reaction to improve CDT effects.

4.1. Light stimulation to speed up Fenton reaction

As a commonly used external stimulus, light possesses the unique characteristics of a controllable wavelength and intensity, as well as an adjustable spot area. Moreover, the relatively low cost, availability and noninvasiveness also make light stimulation more appealing. Many studies have examined tumour imaging and therapies using light-triggered nanomaterials, such as photoacoustic imaging, upconversion fluorescence imaging, photothermal therapy (PTT), photodynamic therapy (PDT) and light-responsive drug release for chemotherapy. Ultraviolet (UV) light promotes the Fenton reaction, which is recognized as a photo Fenton reaction. Thus, the participation of UV light would also enhance CDT efficiency. Due to the damage to normal tissues and the extremely low penetration depth of UV light, near-infrared light (NIR) is typically combined with upconversion nanomaterials (UCNPs) as UCNPs could convert NIR into UV/Vis, which has also been applied frequently in nanomedicine.
Based on the above considerations, our group developed a nanoplatform, NaYF₄:Yb³⁺,Tm³⁺@NaYF₄@dSiO₂@mSiO₂-Ru²⁺/Fe²⁺ (UCSRF), featuring mitochondrial DNA targeting that generates ROS via an NIR-triggered photo Fenton reaction. As shown in Figure 7a, the UCNP cores converted NIR to UV/Vis, and the mesoporous silica shell loaded and delivered the Fenton agent and Ru²⁺ complex on the surface to bind the mitochondrial DNA. When irradiated with NIR, the generated ·OH would destroy the mitochondrial DNA. The bio-TEM image with the corresponding energy dispersive spectrum (EDS) (Figure 7b) and the CLSM (Figure 7c) images all clearly proved that the mitochondria were the preferred cellular target of UCSRF. Compared with the phosphate buffer saline (PBS) control, PBS with NIR irradiation, UCS-Ru²⁺/Fe²⁺ alone, UCS-TPP/Fe²⁺ with NIR irradiation and UCS-Ru²⁺/Fe²⁺ with UV irradiation groups, the UCS-Ru²⁺/Fe²⁺ with NIR irradiation group exhibited the strongest green fluorescence, indicating the highest level of ·OH generation (Figure 7d), consistent with the MTT results (Figure 7e). Moreover, tumour growth was inhibited in the UCSRF-treated group (Figure 7f and 7g). Although the study did not directly utilize NIR light, it provided the foundation of introducing NIR to enhance the CDT efficiency.

4.2 Heat stimulation to speed up Fenton reaction
As another external energy field, heat has also been reported to promote CDT using FeS₂-PEG nanoparticles (Figure 8a).\(^{59}\) The synthesized FeS₂-PEG nanoparticles generated localized heat in a photothermal conversion process using an NIR laser. Subsequently, the heat accelerated and enhanced the Fenton reaction for amplified CDT. Figure 8b showed the electron paramagnetic resonance (EPR) spectra and the results obviously revealed the ability of heat to promote the Fenton reaction. Moreover, the FeS₂-PEG nanoparticles exhibited sufficient performance in MB decolourization (Figure 8c), as the degradation ratio improved when heat was introduced. The image captured after the administration of different treatments shown in Figure 8d revealed that the FeS₂-PEG nanoparticles substantially suppressed tumour growth after NIR irradiation, which was ascribed to the synergistic effect of PTT and heat-enhanced CDT. Although heat was generated indirectly via NIR laser radiation, the results still provided evidence for the ability of heat to enhance CDT and propel interests of developing other heat-enhanced CDT nanomaterials.

5. Conclusions and outlook

The side effects of traditional chemotherapy and radiotherapy technology on patients cannot be ignored. Therefore, many researchers have focused on combining these treatments with nanotechnology and developed novel treatment methods. Under the direction of this pursuit, CDT has emerged as a new “green” treatment displaying selectivity and specificity, and represents a further development of the mechanism of chemotherapy and radiotherapy. More importantly, CDT combines the TME and classical Fenton reaction or Fenton-like reaction and then destroys the tumour in situ, holding potential for clinical translation. To date, many studies have reported new nanomaterials that regulate the Fenton reaction in a particular environment and use external energy fields, all of which have promoted the development of CDT nanomaterials in biomedicine.

This minireview summarizes the current development of the field of CDT (in situ treatments using the Fenton reaction or Fenton-like reactions to generate ·OH in tumour sites), including the selection of nanomaterials, the regulation of the reaction environment, and the introduction of an external energy fields as stimulus (including light, heat, etc.) to improve the CDT efficiency. These strategies are all based on the principle of CDT and are discussed in depth, with an emphasis on the design and implementation of the ideas. Nevertheless, CDT is still in its infancy. Additional studies are required before CDT is ready for clinical translation, as some important scientific issues must be considered. Representative issues are listed below.
First, in-depth explorations of the anticancer pathways of CDT using genetic and molecular methodologies are required for further CDT optimization. Second, the specificity or biocompatibility of CDT must be improved to prevent potential damage to normal cells, because the pH of lysosomes in normal cells is also low and would promote ·OH generation, even if the concentration of hydrogen peroxide is very low. Third, the targeting efficiency of CDT agents for tumour tissues should be improved and it is a common challenge for all nanomaterials. Moreover, unified diagnostic and treatment guidelines for different diseases should be developed. Thus, it is urgent to introduce advanced diagnostic methods (such as computed tomography imaging, magnetic resonance imaging or positron emission computed tomography imaging) to achieve real-time monitoring and an assessment of CDT effect. Finally, the most crucial issue is to increase the ·OH amount in situ in the tumour area during the CDT process. Several feasible strategies have been proposed as responses to these challenges and the details are presented below. Last but not the least, the development of nanomaterials should consider both the functionality and easy synthesis procedures as we want to apply them in the real world.

The fields of catalysis and environmental protection might be the source of guidelines for the selection of nanomaterials, as certain polyoxometalates (POMs) serve as pH-independent agents that induce Fenton-like reactions. In addition, MOFs provide extensive choices for CDT such as selecting suitable Fe³⁺ MOFs for magnetic resonance contrast agents when playing roles in CDT and the surface of iron-based MOFs could be easily functionalized for demand CDT. Second, we may increase lactic acid accumulation by inhibiting aerobic glycolysis using strategies that reduce the oxygen content in tumour to reduce the TME pH. Furthermore, metal-based peroxides, which are acid-sensitive agents, should be considered to substantially increase the amount of H₂O₂ for efficient CDT. With the introduction of an external light field, UCNPs will facilitate the generation of ·OH of CDT agents, as it could convert NIR to UV to promote Fenton-like reactions. Moreover, MOFs could also be used for assistant phototherapy when act as CDT agents under light irradiation.

A magnetic field has been shown to stimulate heat production from magnetic nanomaterials and indirectly enhance CDT efficiency. Some unstable molecules containing peroxo bridges also produce H₂O₂ under sonication to enhance the ·OH production during CDT. CDT would also adequately exert its potential when applied in combination with clinical radiofrequency ablation technology, which utilizes an electric field to produce hyperthermia. In summary, CDT is a flourishing research frontier that requires further exploitation, despite the presence of several unresolved issues. Finally, our hope is to pursue and design optimal nanomedicines with on-demand CDT efficiency combined with advanced diagnostic methods to provide specific, efficient and safe protocols for treating cancer or other diseases and improving patient health.

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Recent rapid developments in chemodynamic therapy using Fenton reactions or Fenton-like reactions to generate ·OH at tumour sites are discussed in depth in this minireview, with an emphasis on the strategies designed to enhance therapeutic efficiency, providing guidelines for potential clinical translation.
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