Perspective

Quazi T. H. Shubhra*

Iron oxide nanoparticles in magnetic drug targeting and ferroptosis-based cancer therapy

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Abstract: Iron oxide (IO) nanoparticles (NPs) have gained significant attention in the field of biomedicine, particularly in drug targeting and cancer therapy. Their potential in magnetic drug targeting (MDT) and ferroptosis-based cancer therapy is highly promising. IO NPs serve as an effective drug delivery system (DDS), utilizing external magnetic fields (EMFs) to target cancer cells while minimizing damage to healthy organs. Additionally, IO NPs can generate reactive oxygen species (ROS) and induce ferroptosis, resulting in cytotoxic effects on cancer cells. This article explores how IO NPs can potentially revolutionize cancer research, focusing on their applications in MDT and ferroptosis-based therapy.

Keywords: magnetic nanoparticles; ferroptosis; drug targeting; cancer

Introduction

Iron oxide (IO) nanoparticles (NPs) have emerged as a highly promising tool in the field of biomedicine due to their unique properties and size. IO NPs demonstrated effectiveness in various biomedical applications, including drug delivery, magnetic resonance imaging (MRI), and hyperthermia therapy [1]. Because of their ability to assist in magnetic drug targeting through external magnetic fields, IO NPs are quite promising and widely used DDS for targeting various tumors to achieves different types of cancer therapies. Apart from their role in drug delivery and imaging, IO NPs can also generate reactive oxygen species and ferroptosis, which can also kill cancer cells to result in impressive therapeutic outcome when properly designed. IO NPs typically undergo degradation at low pH environments, wwhich leads to the formation of iron ions. These iron ions can then react with hydrogen peroxide (H_2O_2) to produce highly reactive ROS, as described in reactions (1)–(3). These ROS can harm cellular components such as DNA, leading to cell death. In this perspective, the potential of IO NPs to revolutionize cancer research is highlighted through the systematic discussion of two intriguing applications: MDT using EMFs and ferroptosis-based cancer therapy. However, the use of IO NPs for drug targeting without EMFs, such as via peptides or aptamers, is not within the scope of this perspective.

$$\text{IO NP} \xrightarrow{\text{Low pH}} Fe^{2+/3+} \quad (1)$$

$$Fe^{2+} + H_2O_2 \xrightarrow{\text{Fenton reaction}} Fe^{3+} + OH^- + \cdot OH \quad (2)$$

$$Fe^{3+} + H_2O_2 \xrightarrow{\text{Fenton reaction}} Fe^{2+} + H^+ + \cdot OOH \quad (3)$$

Iron oxide nanoparticles in drug targeting using external magnetic fields

Unlike several other NP variants, IO NPs can be guided to the tumor site with the aid of an EMF, without the need for surface immobilization of targeting agents like peptides, aptamers, proteins, or antibodies. However, similar to other NP types, it is crucial to coat the bare surface of IO NPs (for example, with polymers or cell membranes) to prevent opsonization and aggregation, and evade macrophage uptake, so that they can reach the tumor site (Figure 1A) [2]. There are two strategies to employ MDT using IO NPs: direct drug conjugation to IO NPs or drug conjugation to a DDS that is co-loaded with IO NPs. While the magnetic field strength plays a key role in MDT using IO NPs, other parameters such as blood flow rate, the surface charge of NPs, or their sizes can also have a significant impact on the final accumulation of NPs. The magnetic field gradient can cause IO NPs to move towards the area of strongest magnetic force (F), as described by equation (4) [3]:

$$F = m \cdot \bigtriangledown B \quad (4)$$

where, m=magnetic moment of an IO NP, B=magnetic field, and ∇ stands for a gradient.

***Corresponding author: Quazi T. H. Shubhra**, Department of Neurosurgery, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China; and Institute of Chemistry, University of Silesia in Katowice, 41-500 Chorzów, Poland, E-mail: shubhro.du@gmail.com. https://orcid.org/0000-0003-4791-2763

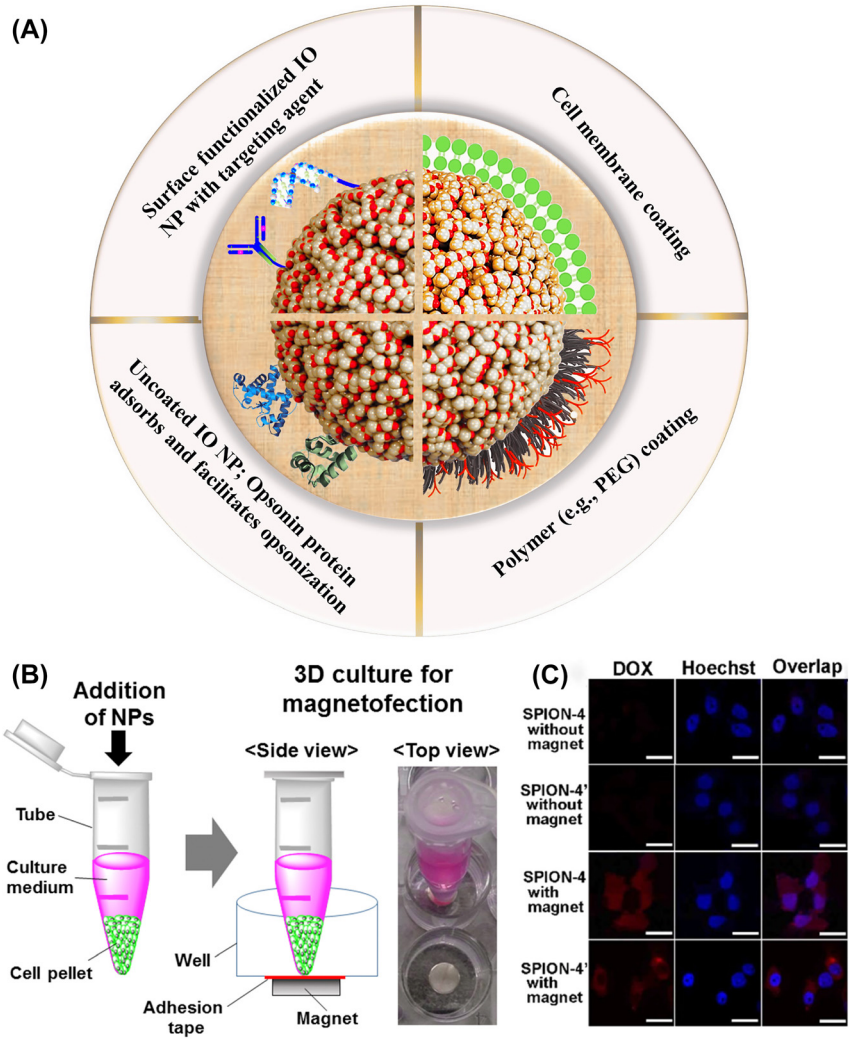

Figure 1: Utilization of iron oxide (IO) nanoparticles (NPs) in magnetic drug targeting (MDT). (A) An IO NP with possible surface functionalization required for MDT. (B) Schematic illustration showing *in vitro* MDT. Reproduced with permissions from ref [4]. Copyright 2017 Elsevier. (C) Confocal images showing delivery of Doxorubicin (Dox) with and without EMF. Reproduced with permissions from ref [5]. Copyright 2021 American Chemical Society. PEG, polyethylene glycol; SPION, superparamagnetic iron oxide.

Researchers utilize an external magnet placed in close proximity to the target site to achieve tumor drug targeting via IO NPs. This method is particularly effective for small animal models, such as a mouse model with a tumor under the skin, like melanoma. However, for larger animal models, like rabbits or rats, and to target distant organs like the heart, a stronger magnet may be required, as demonstrated by Liu and colleagues, who utilized a 1,300 mT magnet placed 5 mm away from the target organ [6]. In contrast to *in vivo* targeting, *in vitro* targeting is much simpler and less complicated since IO NPs do not face the biological obstacles encountered in the bloodstream. For *in vitro* targeting, the magnet can be conveniently placed beneath the cell culture plate, as demonstrated by us and shown in Figure 1B [4]. MDT substantially enhances drug internalization in cultured cells/tumor tissues as compared to the non-targeted groups. This can be determined via ICP-MS analysis or observed through techniques such as confocal imaging, tissue staining, etc., as we, Peng et al., and others have demonstrated (Figure 1C) [5, 7]. MDT is a valuable tool for achieving image-guided cancer therapies through the use of MRI, which allows for monitoring the biodistribution of the DDS within the body.

Iron oxide nanoparticles in ferroptosis-based cancer therapy

Recent advances in nanotechnology have propelled cancer treatment to unprecedented heights. Ferroptosis is a regulated cell death process that was identified in the early years of the

last decade. It is characterized by the excessive peroxidation of lipids, which ultimately results in cell death due to membrane damage. The process is triggered by the loss of redox homeostasis and dysregulation of cellular iron levels. IO NPs play a role in ferroptosis induction by generating ROS via a series of reactions (e.g., reactions (1)–(3)), ultimately leading to lipid peroxidation as depicted in Figure 2 [8]. During ferroptosis-based cell death, a series of reactions take place, as depicted in the lower box of Figure 2. The excessive peroxidation of polyunsaturated fatty acids (PUFAs) containing phospholipids (PUFA-PLs) within the cellular membrane causes membrane rupture, ultimately resulting in ferroptosis. Phospholipid hydroperoxides (PLOOHs), a form of lipid-based ROS, undergo chain initiation, propagation, and termination steps, leading to cell membrane damage during ferroptosis. Fe^{2+} plays a crucial role in the initiation step, forming PLO radicals from PLOOHs. Ferroptosis-based cell death has shown potential for the treatment of various cancers, as cancer cells often exhibit "iron addiction" and are more susceptible to ferroptosis than healthy cells [9].

This innovative approach to ferroptosis-based cancer treatment holds great promise for future research, as demonstrated by the work of Yue and colleagues [10]. However, achieving precise targeting of the tumor site and efficient entry into cancer cells are crucial for successful ferroptosis-based cancer therapy. To address these challenges, researchers have developed multifunctional or smart DDSs based on IO NPs, enabling precise drug targeting and triggered release for enhanced therapeutic outcomes based on ferroptosis [11].

Overcoming substantial challenges is necessary to achieve clinical success in MDT and ferroptosis-based cancer therapy, especially for non-superficial cancers. Our initial studies achieved efficient anticancer drug targeting using 240 mT magnets attached to the skin above the tumor area with surgical tapes [12]. However, we subsequently discovered that magnetic targeting alone is not as effective as approaches utilizing aptamers or peptides [13]. Consequently, we have combined magnetic targeting with aptamer/peptide-based targeting to achieve enhanced tumor drug accumulation compared to MDT alone (Figure 1A) [12, 13]. Additionally, we have explored the approach of combining MDT with homotypic targeting using cancer cell membrane (CCM) coating (Figure 1A) [14]. CCM-coating of NPs takes advantage of cell adhesion molecules and others to get "markers of self" along with "self-recognition molecules" to result in homologous targeting. Ongoing research in our lab focuses on combining MDT with homologous and peptide/aptamer-based triple targeting approaches. Furthermore, efficient drug release at the tumor site or inside cancer cells significantly impacts therapeutic outcomes, especially in cases involving ferroptosis. Therefore, triggered release mechanisms utilizing various external or internal stimuli are highly preferred. Laser-based triggered release has been reported in our studies, while Yue et al. have explored ATP/pH-triggered drug release [10, 13]. Investigating a combination of laser

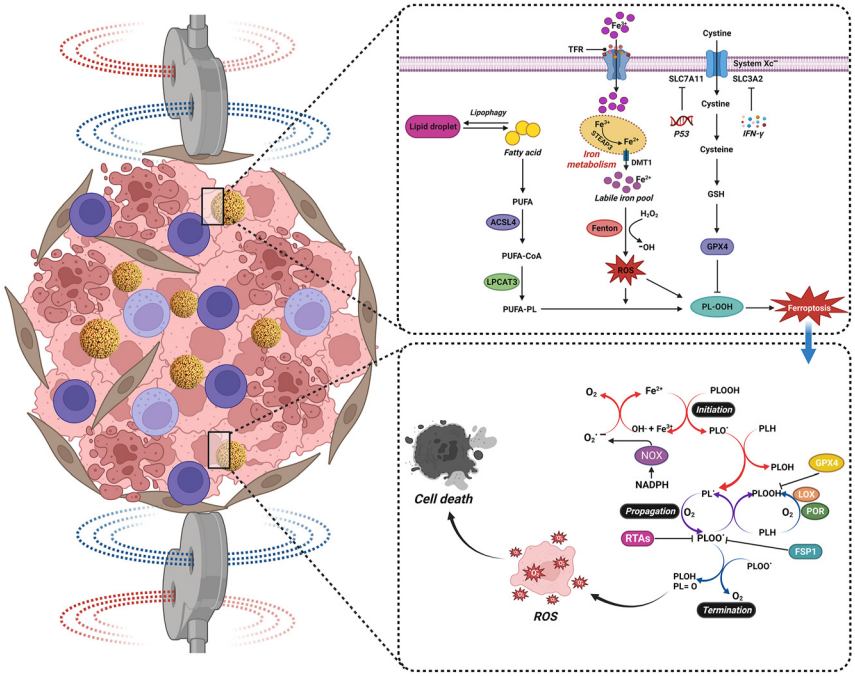

Figure 2: Illustration depicting magnetic drug targeting (MDT) to a tumor with iron oxide nanoparticles (IO NPs) to achieve ferroptosis-based cancer therapy. ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; GPX4, glutathione peroxidase 4; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PLOOHs, phospholipid hydroperoxides; LOX, lipoxygenase; FSP1, ferroptosis suppressor protein 1.

and ATP/pH-triggered release could be an intriguing area for future research.

A key challenge in ferroptosis-based cancer therapy using IO NPs is that inducing ferroptosis with IO NPs alone may not be sufficient for effective tumor treatment. To address this challenge, we are currently investigating the co-delivery of ferroptosis-inducing agents with therapeutic agents, such as Dox. While Dox is known for inducing apoptosis and pyroptosis, recent research has demonstrated its potential to trigger ferroptosis as well [10]. Cells have complex mechanisms to prevent lipid peroxidation, which can suppress ferroptosis. Defense against ferroptosis is governed by system Xc–, glutathione, glutathione peroxidase 4, etc. Their inhibition, such as by blocking system Xc–or consuming glutathione or inactivating glutathione peroxidase 4, can sensitize cells to ferroptosis-inducing agents. Our preliminary studies have shown that drugs like sorafenib or sulfasalazine can inhibit the GSH/GPX4 system, and this inhibition can also be achieved using siRNAs. Zhou and colleagues successfully inhibited breast tumors in a mouse model by combining sorafenib with IO NPs to induce ferroptosis by targeting system Xc– [15]. To achieve efficient ferroptosis, exploring the use of siRNAs in combination with IO-based smart DDSs, in addition to sorafenib or sulfasalazine, could be worth investigating. Furthermore, combination therapy utilizing both apoptosis and ferroptosis approaches may hold potential for effective tumor ablation and highly efficient therapy.

Conclusions

IO NPs hold immense potential for advancing cancer therapies, particularly in magnetic drug targeting and ferroptosis-based treatments. Their capacity for targeted drug delivery through EMFs reduces the risk to healthy tissues, while their ability to induce ferroptosis offers a promising avenue for cancer cell eradication. Ongoing research aims to further optimize IO NPs' applications in these areas, driving advancements in cancer treatment.

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References

1. Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, et al. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol 2016;11:986–94.
2. Fang RH, Gao W, Zhang L. Targeting drugs to tumours using cell membrane-coated nanoparticles. Nat Rev Clin Oncol 2023;20: 33–48.
3. Barbic M. Possible magneto-mechanical and magneto-thermal mechanisms of ion channel activation in magnetogenetics. Elife 2019;8: e45807.
4. Shubhra QTH, Oyane A, Nakamura M, Puentes S, Marushima A, Tsurushima H. Rapid one-pot fabrication of magnetic calcium phosphate nanoparticles immobilizing DNA and iron oxide nanocrystals using injection solutions for magnetofection and magnetic targeting. Mater Today Chem 2017;6:51–61.
5. Peng N, Corpstein CD, Wang Y, Yang M, Hua C, Zou T, et al. Antitumor effects of pH-/Reduction-responsive Fe_3O_4@Alginate magnetic nanoparticles loaded with Doxorubicin on subcutaneous tumor models of hepatocellular carcinoma xenografts in BALB/c nude mice. ACS Appl Nano Mater 2021;4:3707–16.
6. Liu S, Chen X, Bao L, Liu T, Yuan P, Yang X, et al. Treatment of infarcted heart tissue via the capture and local delivery of circulating exosomes through antibody-conjugated magnetic nanoparticles. Nat Biomed Eng 2020;4:1063–75.
7. Liu Y, Guo K, Ding M, Zhang B, Xiao N, Tang Z, et al. Engineered magnetic polymer nanoparticles can Ameliorate breast cancer treatment inducing pyroptosis-starvation along with chemotherapy. ACS Appl Mater Interfaces 2022;14:42541–57.
8. Pan H, Yang S, Wang YE, Shubhra QTH. Ferroptosis-based image-guided chemotherapy. Matter 2023;6:666–8.
9. Hassannia B, Vandenabeele P, Berghe TV. Targeting ferroptosis to iron out cancer. Cancer Cell 2019;35:830–49.
10. Yue R, Zhang C, Xu L, Wang Y, Guan G, Lei L, et al. Dual key co-activated nanoplatform for switchable MRI monitoring accurate ferroptosis-based synergistic therapy. Chem 2022;8:1956–81.
11. Guo K, Liu Y, Ding M, Sun Q, Shubhra QTH. Enhanced drug release from a pH-responsive nanocarrier can augment colon cancer treatment by blocking PD-L1 checkpoint and consuming tumor glucose. Mater Des 2022;219:110824.
12. Liu Y, Ding M, Guo K, Wang Z, Zhang C, Shubhra QTH. Systemic Co-delivery of drugs by a pH- and photosensitive smart nanocarrier to treat cancer by chemo-photothermal-starvation combination therapy. Smart Mater Med 2022;3:390–403.
13. Shubhra QTH, Guo K, Liu Y, Razzak M, Manir MS, Alam AKMM. Dual targeting smart drug delivery system for multimodal synergistic combination cancer therapy with reduced cardiotoxicity. Acta Biomater 2021;131:493–507.
14. Guo K, Liu Y, Tang L, Shubhra QTH. Homotypic biomimetic coating synergizes chemo-photothermal combination therapy to treat breast cancer overcoming drug resistance. Chem Eng J 2022;428: 131120.
15. Zhou H, Lu X, Du C, Zhou Z, Feng J, Liang Z, et al. Cycloacceleration of reactive oxygen species generation based on exceedingly small magnetic iron oxide nanoparticles for tumor ferroptosis therapy. Small 2022;18:2202705.