REVIEW

Surface Engineering of Magnetic Iron Oxide Nanoparticles for Breast Cancer Diagnostics and Drug Delivery

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Abstract: Data published in 2020 by the International Agency for Research on Cancer (IARC) of the World Health Organization show that breast cancer (BC) has become the most common cancer globally, affecting more than 2 million women each year. The complex tumor microenvironment, drug resistance, metastasis, and poor prognosis constitute the primary challenges in the current diagnosis and treatment of BC. Magnetic iron oxide nanoparticles (MIONPs) have emerged as a promising nanoplatform for diagnostic tumor imaging as well as therapeutic drug-targeted delivery due to their unique physicochemical properties. The extensive surface engineering has given rise to multifunctionalized MIONPs. In this review, the latest advancements in surface modification strategies of MIONPs over the past five years are summarized and categorized as constrast agents and drug delivery platforms. Additionally, the remaining challenges and future prospects of MIONPs-based targeted delivery are discussed.

Keywords: Nanopreparations, Organic Nanomaterials, Inorganic Nanomaterials, Surface Engineering, Targeted Delivery

Introduction

Breast cancer (BC) ranks among the top 10 cancers affecting women worldwide. In 2020, the incidence of BC (11.4%) surpassed that of lung cancer (11.1%), establishing it as the most prevalent form of cancer globally. According to the American Cancer Society, new cases of BC in women are projected to account for 31% of all cancer patients by 2023, making it the most prevalent cancer type. Furthermore, BC is identified as the second leading cause of cancer-related deaths among women. During the 1980s and 1990s, BC incidence and mortality reached peak levels.[1] Over the past decade, significant advancements such as the widespread adoption of breast X-ray screening, magnetic resonance imaging (MRI), and neoadjuvant therapies (including tumor plasticity techniques, adjuvant chemotherapy options, immunotherapy approaches, targeted therapy interventions, and endocrine therapy applications) have markedly reduced BC incidence and mortality rates.[2,3] Despite these improvements, global BC incidence and mortality rates continue to rise, alongside regional disparities. For instance, systematic disparities in treatment outcomes and prognosis

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Graphical Abstract
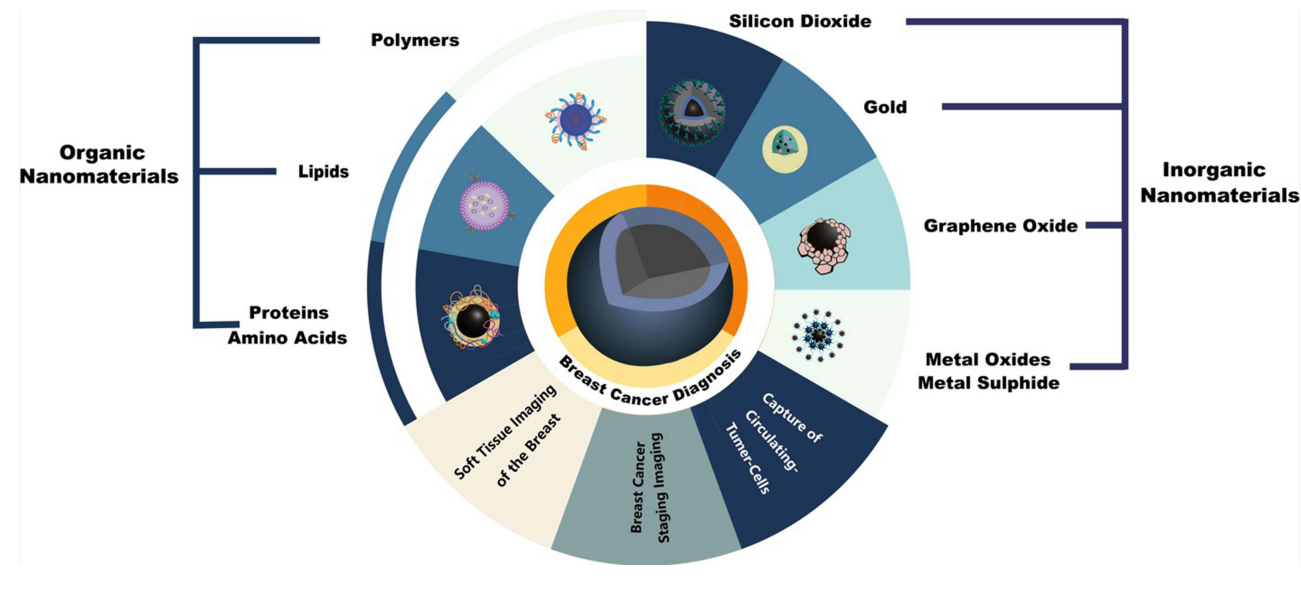
persist, particularly among black women in less developed regions, who experience higher incidences and mortality rates associated with triple-negative breast cancer (TNBC) compared to other racial groups.[4]

According to the tumor scope, the development of BC is primarily categorized into five stages: stage 0: represents carcinoma in situ or non-invasive BC; stage I: indicates a maximum tumor diameter of less than or equal to 2 cm; stage II: corresponds to a maximum tumor diameter of 2–5 cm; stage III: signifies a maximum tumor diameter exceeding 5 cm; and stage IV: denotes BC invasion and metastasis. The treatment of BC depends on individualized clinical characteristics, necessitating the development of effective strategies based on diagnostic results, staging, biological subgroups, genetic factors, genomics characteristics, and individual patient conditions and preferences.[5] Studies have demonstrated that the incidence of BC subtypes is influenced by race and age. HER2-positive BC shows a higher incidence compared to other subtypes while maintaining consistent ratios among racial groups.[4] Hormone therapy or monoclonal antibodies targeting HER2 are commonly employed for BC treatment,[6] whereas TNBC relies on traditional cytotoxic chemotherapy due to the absence of targeted proteins such as estrogen receptors and progesterone receptors. TNBC is characterized by greater aggressiveness compared to other BC subtypes, with an increased recurrence rate and mortality observed during early treatment phases, along with shorter survival times in advanced stages. Early screening, diagnosis, and precision treatment are pivotal in the fight against BC. Extensive data underscores the necessity for developing novel drug-targeting strategies to address the existing challenges in diagnosing and treating BC.

Magnetic iron oxide nanoparticles (MIONPs) targeted delivery system is one of the challenging researches in the field of BC diagnosis and treatment. MIONPs are generally defined as advanced multifunctional nanomaterials consisting of iron oxide nanoparticles and surface modifications that render them biocompatible, biodegradable, and biosafety. The core of MIONPs typically consists of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), with diameters ranging from 1 to 100 nm. Surface modification allows small-sized MIONPs to evade uptake by the reticuloendothelial system (RES), thereby prolonging their circulation time within the body. Furthermore, they can disperse and penetrate the dense internal structure of tumors. However, under normal physiological conditions, they cannot traverse capillary cell gaps. Commonly used preparation methods for MIONPs[7] include thermal decomposition, co-precipitation, flow injection synthesis, microemulsion, sol-gel, hydrothermal methods, and sonochemistry. Among these methods, the thermal decomposition method is considered the industry standard for producing large-scale MIONPs with controllable particle size and uniform dispersion. However, Fe_3O_4 particles prepared through this method exhibit poor water solubility, necessitating further modification

with hydrophilic materials to enhance solubility. The coprecipitation method suffers from limitations in accurately controlling particle size and dispersion. The flow injection synthesis method relies on the regulation of capillary reactor process parameters,[8] making the cost of large-scale production a significant consideration. The crystal composition of iron oxide nanoparticles prepared by the sol-gel method[9] is heavily affected by the annealing temperature and the initial mixture ratio. Although the technology is relatively simple, product stability is a potential challenge.

Various synthetic approaches and surface modification materials influence the physicochemical properties of MIONPs as well as their subsequent biological applications. Factors such as size distribution,[10] nanocrystalline shape,[11,12] nanoparticle arrangement pattern[13] and magnetic parameters[14] are known to affect tumor targeting efficiency, retention performance, and magnetic heating capability. These interactions occur due to the high permeability and strong retention effect (EPR effect) observed in breast tumor tissue, as well as unique physiological characteristics[15] such as vascular system leakage and lymphatic drainage dysfunction associated with tumor tissues.

MIONPs and the Diagnosis and Treatment of BC

MRI is a crucial non-invasive technique for tissue and molecular imaging in the diagnosis of BC. The magnetic resonance signal is an image obtained by spatially arranging the resonance signal of protons in human tissues by gradient magnetic fields. Essentially, it is a density map of protons in human tissues. The transverse magnetization reflected by the magnetic resonance pixel value is not only related to the number of protons, but also to the characteristics of their relaxation process, and the "relaxation time" is described by the time constants "T_1" and "T_2". The relaxation time of normal tissue and diseased tissue usually shows only slight differences and limited contrast. The significance of contrast agents (CAs) lies in their ability to enhance the MR signal by influencing the proton relaxation rate, thereby enhancing the sensitivity and accuracy of MRI. Clinical CAs are categorized into T_1-weighted positive CAs and T_2-weighted negative CAs. This review focuses on MIONPs T_2 CAs with a size exceeding 10 nm. In recent years, there has been growing interest in the research and discussion of ultra-small MIONPs (0–5 nm) as T_1 CAs.[16]

MIONPs significantly shorten the transverse T_2 relaxation time of protons and exhibit a more obvious dark contrast in T_2-weighted MRI. Moreover, owing to the substantial magnetic moment of MIONPs, an enhanced signal-to-noise ratio can be attained at low concentrations, thereby augmenting the resolution of soft tissue MRI. When an external magnetic field is applied to tumor tissue, MIONPs actively or passively accumulate at the tumor site, showing high sensitivity to the tumor. MIONPs are recognized for their excellent capabilities in enhancing MRI contrast[17] biosafety[18] and favorable pharmacokinetic properties,[19] showing substantial potential in the construction of molecular imaging probes for BC.

Clinical Application of Iron Oxide Nanoparticles

Multiple formulations have received FDA approval as clinical diagnostic T_2 CAs, driven by the potential of both intracellular and extracellular research and development. Feridex IV® (Ferumoxides) has been promoted in the field of MRI for liver tumor imaging. In addition, there are lymph node metastasis imaging agents Combidex® (Ferumoxtran-10), gastrointestinal contrast agents Gastromark® (Ferumoxsil), and iron supplements including Feraheme® (Ferumoxytol) are also available.

Feridex IV®

Feridex IV®[20] is a sterile aqueous colloid composed of superparamagnetic iron oxide and dextran, with a particle size of 80–150nm. Following intravenous administration, it is phagocytosed by the RES in the liver, thereby creating a distinct contrast between normal and cancerous liver tissues, and facilitating lesion localization. Early studies utilizing long/short double-echo acquisition of T_2-weighted MRI with ferumoxides enhancement not only yield high-quality images but also enable differentiation of metastases from benign lesions in noncirrhotic livers.[21] In the context of cell therapy, where there is significant interest in the development of cell tracking and repair strategies, it has been demonstrated that in vivo labeling of monocytes with iron increases by twofold when a mixture of ferumoxides and sodium ferric gluconate is used instead of ferumoxides alone. Further relevant animal experiments are expected to establish this approach as an effective means for tracking inflammation in vivo.[22] Moreover, this magnetic marker is capable of tracking the temporal and spatial migration of stem cells and other cellular tissues.[23]

Combidex®

Combidex® is a solution of dextran-coated iron oxide nanoparticles, with particles ranging in size from 20–50 nm, and is approved for clinical lymph node metastasis imaging. Early research results showed that the overall sensitivity (90.5%) of MRI based on Ferumoxtran-10 lymphocyte-affinity superparamagnetic nanoparticles was significantly higher than that of conventional MRI (35.4%) while the diagnostic specificity was improved from 90.4% to 97.8%.[24] In the past two decades, Ferumoxtran-10 has gone from approval to deregistration, was reintroduced to the market in 2013, and has achieved encouraging clinical results in clinical use in patients.[25] For example, in a direct comparison of ultrasmall superparamagnetic iron oxide particle-enhanced MRI (USPIO-MRI) and prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT), USPIO-MRI has shown greater sensitivity in detecting suspicious lymph nodes (LN) <5 mm.[26]

Gastromark®

Gastromark®[27] is a silica-coated superparamagnetic iron oxide suspension, featuring particles sized between 200–400 nm. Unlike other injectable contrast agents, Ferumoxsil functions as a gastrointestinal contrast agent administered orally, remaining unabsorbed by the gastrointestinal tract. Its effectiveness manifests within half an hour post-administration, with excretion occurring via feces within 7–8 hours subsequent to gastrointestinal retention. The findings from two clinical trials involving a total of 186 patients demonstrate that over half of the participants exhibited improved upper gastrointestinal and gastric imaging following the administration of Ferumoxsil for 30 minutes, while also observing enhanced colonic visualization and improved delineation of anatomical markers in MRI scans.[27] Nevertheless, the unpleasant taste of oral iron remains a significant barrier to its widespread clinical use. Furthermore, there is currently insufficient evidence regarding potential drug interactions and distribution in specific patient populations for Ferumoxsil.

Feraheme®

Unlike the majority of iron-based nanoparticles utilized in MRI, Feraheme® has received approval for treating iron deficiency anemia (IDA) commonly observed in patients with renal insufficiency, while concurrently undergoing clinical trials as MRI CAs. Previous preclinical studies have indicated that Ferumoxytol is expected to serve as a promising MR cell tracer in cell therapy, such as tracking Ferumoxytol-labeled stem cells[28] and macrophages[29] by MRI to monitor cell migration and rejection reactions. Results from a small-scale clinical trial's histopathological analysis have validated the clinical feasibility and applicability of Ferumoxytol-enhanced MRI for the quantitative detection, and monitoring of macrophages in tumors.[30] In addition to providing new non-invasive quantitative biomarkers for tumor treatment stratification and assessment of treatment response, studies have demonstrated that Ferumoxytol can induce phenotypic transformation of M2 macrophages into M1 macrophage subtypes characterized by high CD86 and TNFα positivity,[31] and M1 polarization triggers the Fenton reaction, thereby inhibiting BC growth.[32] It can be speculated that Feraheme®-mediated tumor immunomodulation is expected to synergize with chemotherapy and potentially achieve new breakthroughs in clinical practice.

Currently, commercial CAs based on MIONPs are limited by low crystallinity or poor surface modification, thus limiting their widespread adoption in BC diagnosis. MagTrace® (MT), currently in clinical trials, is primarily utilized for sentinel lymph node biopsy (SLN) in early-stage BC axillary staging, aiming to enhance identification rates and diminish complication occurrences.[33] As early as 2013, The SentiMAG Multicentre Trial compared MT with standard techniques (radioactive isotopes with blue dye (BD) or radioactive isotopes alone) for sentinel lymph node biopsy. MT demonstrated a recognition rate of 94.4%, marginally lower (0.6%) than standard methods (95%), with LN retrieval values closer to actual counts.[34] A recent network meta-analysis quantitatively assessed various sentinel lymph node identification techniques and their respective false-negative rates, comprehensively comparing detection and false-negative rates across all methods. Findings indicate that MT outperforms BD alone in lymphatic tracing, exhibiting comparable sentinel lymph node detection and false-negative rates to dual tracer methods.[35]

At present, there are still some SPIO (Small particles of iron oxide) and USPIO (Ultrasmall particles of iron oxide) in the clinical trial stage, as summarized in Table 1.

Table 1 MIONPs-Based CAs in Clinical Trials in the Last Decade

Diseases	Company or Collaborator	Type	Trade name	Purpose	Stage	Time	Literature
BC	Sahlgrenska University Hospital (SUH)	SPIO	MagTrace® (MT)	SLN	II	2023	[36]
	SUH	SPIO	MT	SLN	Ib/II	2022	[37]
	SUH	SPIO	MT	SLN	Ib/II	2021	[38]
	Uppsala University	SPIO	MT	SLN	III	2020	[39]
Non-BC	Poznan University of Medical Sciences	N/A	NanoActivator®	Glioblastoma multiforme	N/A	2024	[40]
	The First Affiliated Hospital with Nanjing Medical University (FAHNMU)	SPIO	Ferumoxytol® (FM)	MRI of cardiac	N/A	2023	[41]
	Peter MacCallum Cancer Centre	SPIO	N/A	Extramedullary Myeloma	I	2023	[42]
	FAHNMU	SPIO	FM	MRI of the renal vascular system	I	2021	[43]
	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	SPIO	FM	MRI of the renal vascular system	I	2021	[44]
	University of Pittsburgh	SPIO	FM	MRI of intravesical	Ib	2021	[45]
	Allegheny Singer Research Institute	SPIO	FM	Primary & Metastatic Hepatic Cancers	Observational	2020	[46]

Application of Iron Oxide Nanoparticles in BC Diagnosis and Treatment

MIONPs possess integrated design capabilities for optimized imaging, cell tracing, and targeted therapy. This combination renders MIONPs an ideal platform for both BC diagnosis and treatment. The MRI enhancement effect of MIONPs significantly depends on the size of the nanoparticle,[17] aggregation state,[47] and surface conjugates, impacting their biocompatibility and MRI effect. Studies have demonstrated that cubic nanoparticles exhibit superior performance in terms of crystallinity, single crystal size, saturation magnetization, and T_2 relaxation rate compared to spherical nanoparticles of the same size.[48] These high-quality nanocrystals hold great potential as candidates for diagnostic imaging and treatment in BC.[49] For instance, ^{225}Ac radionuclide-labeled MIONPs (^{225}Ac@Fe$_3$O$_4$-CEPA-trastuzumab) can serve as a valuable tool for fluoroscopy in HER2-positive BC, combining trastuzumab with α-radioimmunotherapy and magnetic hyperthermia.[50] NO-responsive MIONPs nanoprobes,[51] modified with o-phenylenediamine (OPA) on the surface, are capable of monitoring dynamic changes in the phenotype of M2/M1 macrophages in tumors, offering insights into the prognostic evaluation of cancer treatments based on macrophage-mediated immune responses. Additionally, superparamagnetic iron oxide nanoparticles (SPIONs) are capable of replacing traditional radioactive substances such as Technetium-99m (Tc99) and BD for SLN detection and localization in primary BC metastasis assessment,[33,52,53] enabling completion with an ultra-low dose intradermal injection method[54] while improving sensitivity, specificity, and accuracy compared to conventional approaches.[55] Another critical marker for tumor metastasis is circulating tumor clusters (CTC). The tracking, capture, and elimination of CTC can be facilitated by MIONPs leveraging cancer cell-related biomarkers or the electrostatic binding affinity between cancer cells and positively charged surfaces[56] (Figure 1). Furthermore, the comprehensive diagnostic strategy of combining MRI with magnetic particle imaging (MPI), fluorescence molecular imaging (FMI), or near-infrared fluorescence imaging (NIRF) of MIONPs, based on their unique size and adjustable functional composition, is paving the way for advancing BC prevention and treatment.[57]

Representative applications of MIONPs applied to BC diagnosis are outlined in Table 2.

More importantly, the inherent Brownian and Neel relaxation mechanisms of MIONPs efficiently convert the energy of an alternating magnetic field (AMF) into thermal energy, resulting in significant thermal effects.[67–70] Within the treatment range, temperatures can be elevated to a range of 42–46 °C.[71] Local temperature extremes are poorly tolerated by tumor cells, leading to protein denaturation,[72] increased permeability of cell membrane,[73] swelling of cell organelles,[74] and DNA damage[75] irreversible damage, with little or no effect on normal tissue.[76,77] These findings strongly support the effectiveness of MIONPs-based magnetic hyperthermia (MHT) as a promising physical anti-tumor modality[78] (Figure 2). Furthermore, the incorporation of one or more therapeutic drugs onto the surface of MIONPs represents a promising strategy for targeted drug delivery in cancer treatment. Nevertheless, suboptimal MHT and combined drug therapy approaches may yield unintended consequences: concurrent drug administration can lead to
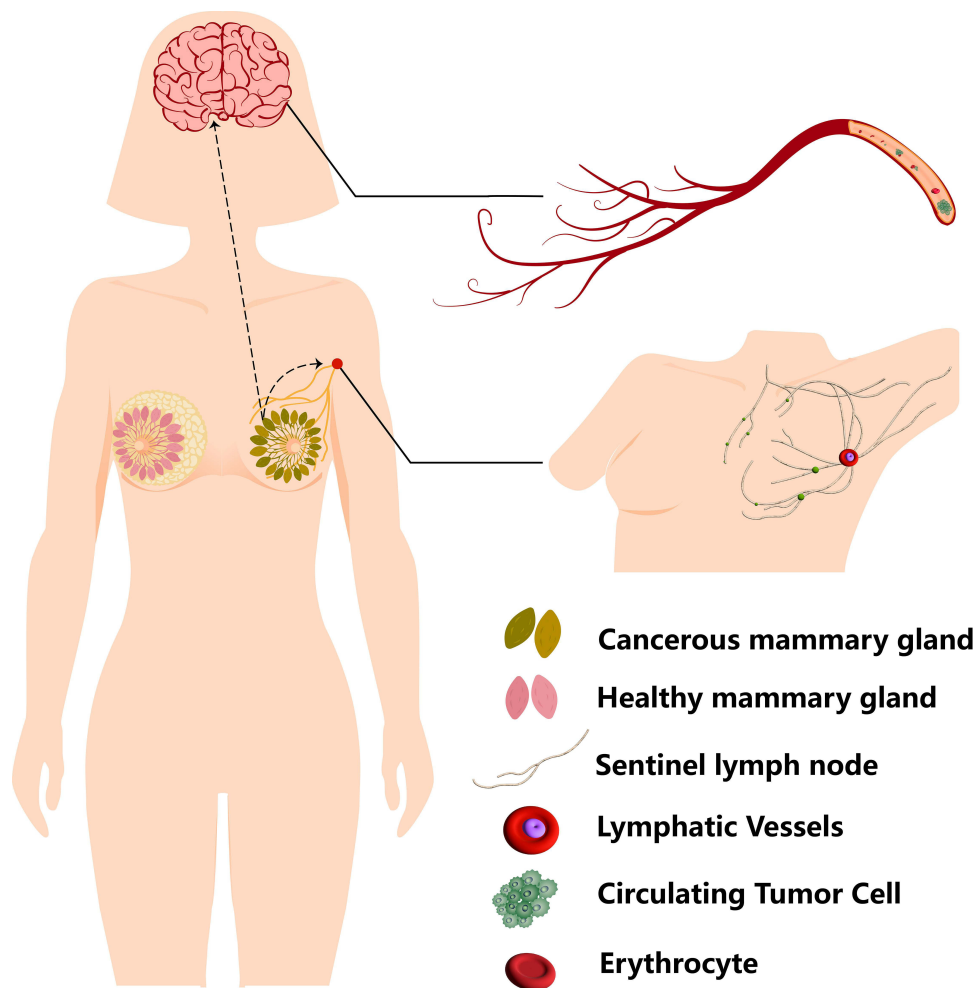
Figure 1 Schematic diagram of brain metastasis and sentinel lymph node metastasis of BC.

multidrug resistance,[79] while excessive heat shock protein exposure may promote cancer metastasis.[80,81] Designing precise and controllable strategies for combining magnetic hyperthermia with drug therapies is crucial to addressing issues such as low efficacy, drug resistance, aggressiveness, and recurrence commonly encountered in BC treatment.

Table 2 Summary of Representative Applications of MIONPs

Active targeting strategy	Appliance	Literature
BRBP1 peptide	MRI/NIRF - Early diagnosis of BC brain metastases	[58]
CREKA peptide (Cys-Arg-Glu-Lys-Ala)	FMI/ MPI - Early diagnosis of BC lymph node metastases	[59]
Anti-human HER2 antibody	Selective isolation of HER2-positive BC cells in the context of HER2-negative BC cells and enumeration	[60]
Anti-EpCAM antibody	Rapid detection and capture of CTC in the blood of BC patients	[61]
Anti-Human EpCAM biotinylated antibody, anti-Human N-cadherin biotinylated antibody	Rapid detection and capture of epithelial CTC and mesenchymal CTC in whole blood samples	[62]
CREKA peptide	Tissue Protease B (CTSB) Trigger Activated Diagnostic Therapeutic Nanoprobes	[63]
RGD peptide	Monitoring the applicability of antiangiogenic agents in an in vivo BC model	[64]
Gd(III) ions, transferrin (Tf)	T_1 Efficient Targeted Contrast Agents for Weighted Positive MRI	[65]
N$_3$-Lys-bell toad peptide	Dual-modality MR/Near Infrared Fluorescence Imaging (MR/NIRFI) contrast agent	[66]

Iron-based Magnetic Nanoformulation

Breast Cancer Cells

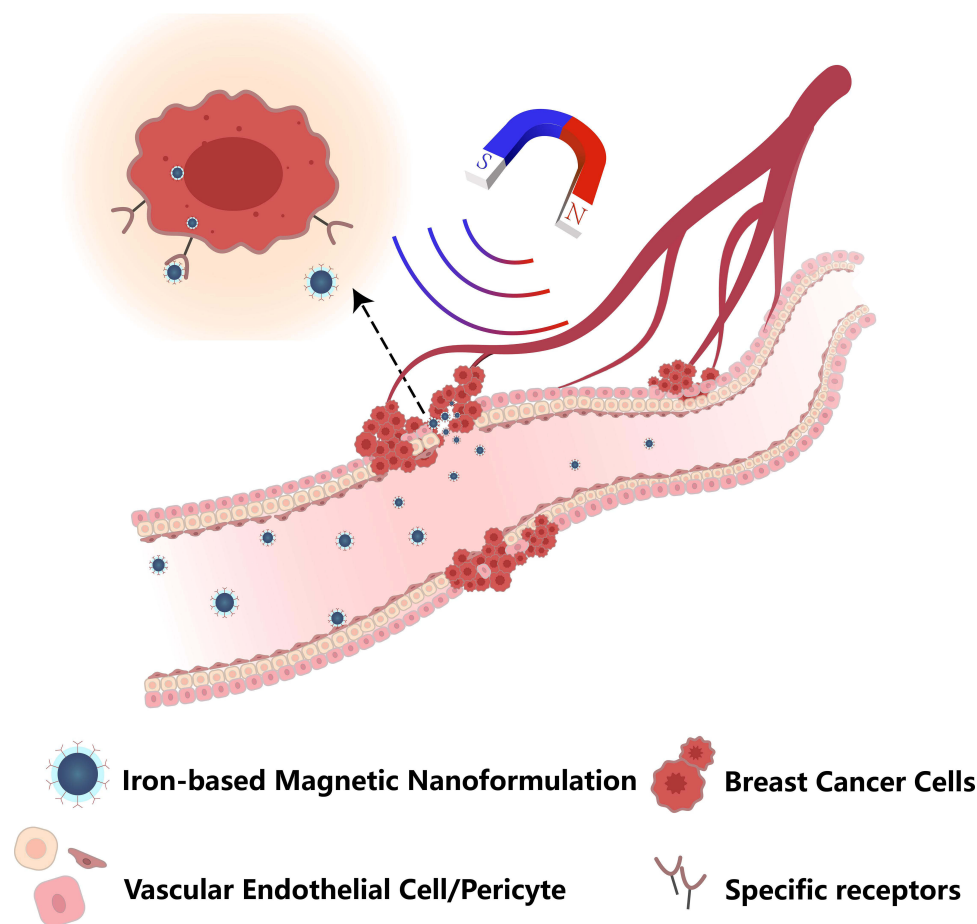**Vascular Endothelial Cell/Pericyte**

Specific receptors

Figure 2 Schematic diagram of targeted drug delivery for magnetothermal therapy.

Targeted delivery system based on surface modification of MIONPs exhibits significant potential as an advanced platform for early clinical diagnosis, real-time imaging, and precision adjuvant therapy of BC, owing to its inherent MRI, biocatalytic activity (nanoenzymes), MHT, and homologous targeted delivery of chemotherapeutic and gene therapy drug.[47]

Surface Engineering of MIONPs

Most iron oxide nanoparticles are inherently hydrophobic, necessitating surface modification for biomedical applications. The targeting strategies for nanoparticles encompass passive targeting via the enhanced permeability and retention (EPR) effect, and active targeting relying on specific targeting ligands. Challenges at the tumor site, such as uncontrolled angiogenesis, high interstitial pressure, dense tumor cells, and the extratumoral matrix, impede drug penetration to the tumor core and hinder optimal drug efficacy. Achieving targeted tumor delivery involves four critical steps: effective retention, phagocytosis evasion, precise targeting, and controlled release. MIONPs leverage an external magnetic field for guided navigation. The modified material coating the iron core acts as a carrier, enhancing biocompatibility and providing docking sites for drugs, fluorescent markers, proteins, enzymes, anti-bodies, or nucleic acids[82] that bind to tumor cell-specific receptors. By navigating the intricate tumor microenvironment and evading macrophage phagocytosis, MIONPs accumulate significantly in target tissues and facilitate rapid drug release directly into deep-seated lesions. This targeted accumulation minimizes off-target site deposition, while also preventing nanoparticle aggregation under physiological conditions, thus avoiding potential blockages in blood vessels.[83]
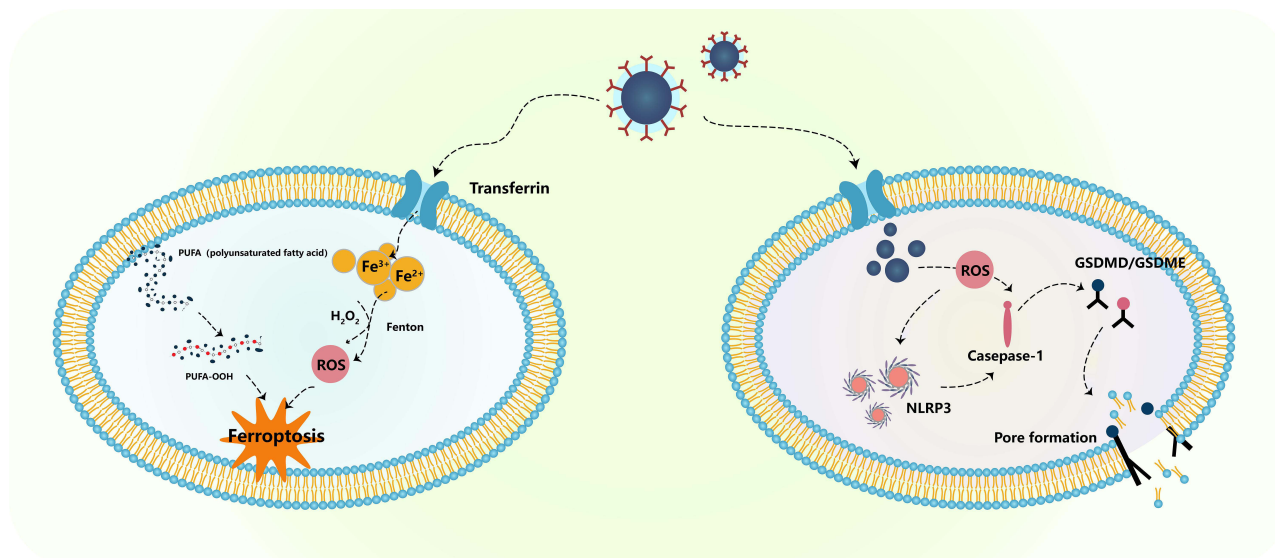
Figure 3 MIONPs mediate iron death/cellular scorch death.

Meanwhile, leveraging their inherent enzymatic catalytic activity, MIONPs can facilitate the conversion of endogenous H_2O_2 into reactive oxygen species (ROS), thereby triggering a novel iron-dependent form of programmed cell death known as ferroptosis. The hydrodynamic diameter, surface charge, morphology, surface coating, and modifications play pivotal roles in modulating the intrinsic enzymatic catalytic activity of MIONPs. For example, a magnetic near-infrared nano-photosensitive micelle (CSO-SS-Cy7-Hex/SPION/Srfn) was developed as a strategy for tumor imaging-guided ferroptosis therapy (FT). Excess lipid peroxides (LPO) accumulate through three pathways: mitochondrial membrane oxidation/reduction reactions, depletion of GSH by disulfide bonds, SPION-induced release of Fe^{2+} initiating the Fenton reaction, and near-infrared light irradiation. Ultimately, these processes trigger mitochondrial collapse and irreversible ferroptosis.[84,85] The unique dual therapeutic approach combines an aldehyde dehydrogenase inhibitor targeting cancer stem cells (CSCs) with ferroptosis, effectively eliminating malignant breast tumors by enhancing ferroptosis through glutathione (GSH) depletion.[86] Additionally, surface-engineered MIONPs induce tumor cell pyroptosis. For example, the virus spike tumor-activated hyperthermia agent (VTPA) accumulates at tumor sites via systemic circulation, triggering intracellular lysosomal rupture and release of iron cores that induce ROS production. Lysosomal rupture and ROS synergistically activate the caspase-1 pathway, leading to the cleavage of Gasdermin family members (such as GSDMD, GSDME), ultimately disrupting the plasma membrane of cancer cells[87,88] (Figure 3).

The surface modification of the nucleus of MIONPs can lead to nanoparticles that can be used for specific applications (targeting specific tissues, loading drugs, and inducing exogenous biological processes). For example, organic polymers can provide MIONPs with excellent biocompatibility and loading capacity, and inorganic small molecule coatings can improve MIONP stability and control size distribution. The modification of nanoparticle surfaces with natural products, polymeric, organic, or inorganic coating was made by one-pot or layer-by-layer methods. Different types of reactions were used for modified IONPs surface, such as click chemistry,[89] UGI multicomponent reaction,[90] bioconjugation,[91] and others.[92] Therefore, This review summarized the recent progress of various organic and inorganic molecules as surface engineering materials for MIONPs.

Organic Nanomaterials
Polymers
Polymer-encapsulated MIONPs have been extensively investigated as an exceptional drug carrier with their remarkable performance. Their advantages can be summarized as follows: (1) Drug delivery assisted by an external magnetic field using a magnetic core surpasses the limitations of traditional diffusion and transmembrane transport methods. (2) The polymer

coating exhibits excellent biocompatibility, ensuring prolonged circulation time of drugs and enhancing specific anticancer drug concentrations at tumor sites compared to other locations by facilitating interaction with target molecules on nanocarrier surfaces. (3) Prevention of spin disorder, uncontrolled oxidation, and nanoparticle aggregation improves the stability of nanoformulations. (4) Bio-based polymers are cost-effective and less toxic, promising for future industrial production.

Polyurethane

Polyurethane (PU)[93] is a well-established biocompatible and blood-compatible biomaterial. Nevertheless, the hydrophobic nature of PU surfaces renders them prone to nonspecific protein adsorption and platelet adhesion, potentially resulting in the formation of blood clots.[94] Techniques for surface modification, such as isocyanate chemical coupling, surface plasma modification, and hydrogen bond interaction, are employed to confer upon PU the ability to resist nonspecific antigen adhesion.

Waterborne polyurethane is an innovative green polyurethane system that utilizes water as a dispersion medium instead of organic solvents. This approach offers several advantages, including cost-effectiveness, safety, and non-toxicity. The main chain of waterborne polyurethane effectively stabilizes hydrophobic drugs through electrostatic forces, playing a unique role in drug delivery. When iron oxide nanoparticles are incorporated into the PU matrix, they can provide structural support for the matrix. The polyurethane structure exhibits high elasticity, good conductivity, magnetizability, and other properties, making it suitable for utilization as a novel composite nanomaterial to enhance MRI quality.[95] The most crucial aspect is that their integration confers magnetic and antibacterial properties[96] to the polymers, enabling them to catalyze Fenton-like and Haber-Weiss reactions, leading to oxidative stress and cellular damage. For example, aqueous polyurethane-based nanomicelles co-encapsulated with hydrophobic SPIONs and the anticancer agent doxorubicin (DOX) exhibited good superparamagnetic behavior and magnetic responsiveness,[97] and experimental results showed that the MRI contrast effect was concentration-dependent.

Despite the benefits of various surface modification technologies in augmenting the biological functionalities of PU-coated MIONPs, persistent challenges exist: (1) Modified polymers may degrade due to exposure to the multifactorial body environment, necessitating further investigation into long-term stability and durability; (2) The chemical coupling method could potentially induce cytotoxicity due to incomplete reactions, necessitating safety evaluation; (3) Ensuring the reproducibility in clinical settings and stable large-scale industrial production technology remains crucial.

Polyethylene Glycol

Modified MIONPs with polyethylene glycol (PEG) is a widely employed strategy. PEG, being a flexible hydrophilic polymer capable of forming segments and densely bound chains,[98] serves as an effective tool for extending drug circulation in vivo and safeguarding therapeutics against adverse immunogenicity.[99] Moreover, the spatial repulsion effect of PEG chains confers an advantage in enhancing drug stability.[100] Siloxane crosslinked PEG-coated MIONPs with small particle sizes release 50% of the drug within the first 4 hours and completely release all drugs within 10 hours in a weak acidic environment, effectively achieving controlled drug release[101] (Figure 4). The PEG coating not only shields nucleic acid drugs from degradation in the body but also enhances their accumulation at tumor sites through increased aggregation. For example, CaP/PEG-polyanion/siRNA magnetic composite nanoparticles (MHNPs) were prepared with CaP serving as an interlayer to enhance biocompatibility, and polyethylene glycol-polyaspartic acid (PEG-PAsp) as an outer stabilizer layer for delivering siRNA targeted to the cytoplasm of BC cells. MHNPs effectively reduced the expression of tumor cell vascular endothelial growth factor (VEGF) compared to free siRNA.[102] Magnetic nanoparticles, based on calcium phosphate-polyethylene glycol block copolymer (CaP-PEG) and coated with caffeic acid (Caf-MCaP), were synthesized by using a co-precipitation method, resulting in a nearly neutral surface zeta potential. Magnetization curves demonstrated that Caf-MCaP exhibited superparamagnetic behavior and low coercivity. By encapsulating siRNA within CaP-PEG, efficient delivery across biological barriers to the cytoplasm of tumor cells was achieved under magnetic guidance, leading to enhanced silencing of the HER2 gene.[103]

It is well known that drug-targeted controlled release largely hinges on the interaction between the bound ligand and the receptor specifically expressed at the molecular level on the target site. However, the receptor-guided strategy faces several disadvantages, including cancer cell heterogeneity,[104] and the presence of binding site barriers.[105] Combining
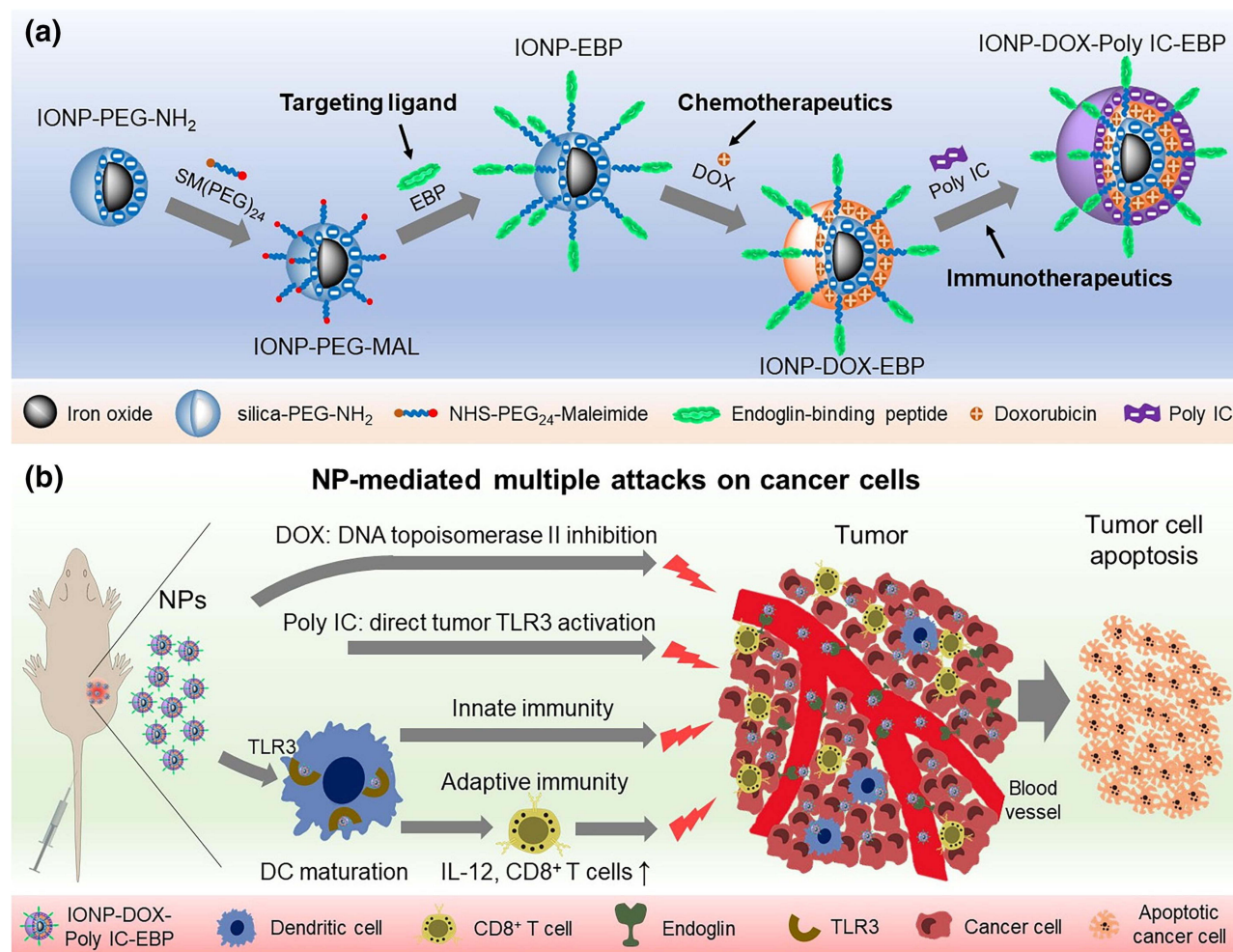
Figure 4 (**a**) Schematic illustration of preparation of the EBP-modified and DOX/Poly IC loaded nanocarrier. (**b**) Mechanisms of targeted and combined chemo-immuno therapy for TNBC. Reprinted from *Materials Today*. Volume 50. Mu Q, Lin G, Jeon M, et al. Iron Oxide Nanoparticle Targeted Chemo-Immunotherapy for Triple Negative Breast Cancer. Page numbers: 149–169. Copyright (2021), with permission from Elsevier.[101]

PEG surface modification with physiologically triggered drug release mechanisms (such as pH or enzyme concentration) represents an optimization strategy to overcome these challenges. A SiO$_2$-modified MRI probe covered with a PEG functionalized coating, and established a pH-responsive intelligent system through pH-low insertion peptide (pHLIP) modification. Histological analysis revealed that the additional pHLIP-modified MNPs were localized in the amphisomes, autolysosomes, and multilamellar bodies within the tumor acidic microenvironment.[106]

Although PEGylation is considered the "gold standard" for surface modification of iron oxide nanoparticles, within the complex pathophysiological environment of BC, the interaction between PEG and plasma proteins critically regulates circulation time, biodistribution, drug release, and immunotoxicity of MIONPs. Challenges arising from these interactions should not be underestimated. The first is the ubiquitous IgM adsorption.[107] PEG-functionalized MIONPs may be naturally recognized as potential pathogens by IgM while entering the bloodstream. This recognition prompts splenic B lymphocytes to produce anti-PEG IgM antibodies, which in turn activate complement and trigger the mononuclear phagocyte system (MPS), resulting in accelerated blood clearance (ABC). Secondly, there is a propensity to induce adverse reactions, notably hypersensitivity reactions. Third, the protein corona formed by the adsorption of PEG and plasma proteins may significantly change the colloidal stability and biological fate of nanoparticles, such as shielding the targeting affinity of specific antibodies and ligands, known as the "off-target effect".[108] To mitigate adverse clinical reactions, attention must be directed towards understanding the specific immune responses elicited by PEG coating, encompassing its physiological induction mechanisms and the impact of structural characteristics of PEGylated nanoparticles.[109]

Carbohydrate Polymers

Carbohydrate polymers[110] are distinguished by their extensive surface area, biodegradability, and environmentally friendly properties, rendering them promising support materials for iron oxide nanoparticles.

Carbohydrate polymers can be categorized into three main groups: (1) natural polysaccharides, (2) synthetic polysaccharides derived from natural sources, and (3) sugar polymers. The combination of carbohydrate polymers with iron oxide nanocores results in the manifestation of distinctive biological activities, including the silencing of carcinogenic epidermal growth factor receptors,[111] antibacterial properties, enhanced immunogenicity,[112] and targeted delivery to tumor cells.[113] β-cyclodextrin (β-CD) with poly (D, L-lactic acid-co-glycolide) PLGA were conjugated by using chemical functional groups to develop a biodegradable polymer with a high drug loading capacity. This highly efficient magnetic carrier has an average size of 30 nm. Both the β-CD cavity and the polymer chain are capable of binding camptothecin. Experimental data demonstrate that the drug encapsulation rate can reach 89%. In addition, PLGA has the characteristics of pH responsiveness and photothermal responsiveness. The sustained release of camptothecin in vivo is facilitated by an external magnetic field in conjunction with the weakly acidic microenvironment of BC, ensuring the maintenance of an effective drug concentration.[114] While the efficacy of the preparation has been confirmed in in vitro experiments involving folate receptor-overexpressing MCF7 cells, further studies are required to assess its in vivo effectiveness. Agar, a linear polymer composed of 1,3-linked β-D-galactose and 1,4-linked 3,6-endoether-L-galactose units, can form chelates with metal ions in a strongly alkaline environment, utilizing its free hydroxyl groups. The cytotoxicity of composite nanoparticles (Fe_3O_4/agar/Au NPs), created by coating the surface of MIONPs with a biopolymer consisting of gold ions and agar, demonstrates a concentration-dependent pattern. Comparison of IC_{50} values of Fe_3O_4/agar/Au NPs across various cell lines, including breast adenocarcinoma (MCF-7), breast cancer (Hs 578Bst), invasive ductal carcinoma (Hs 319.T), and metastatic carcinoma (MDA-MB-453), reveals that the Hs 319.T cell line exhibits the highest cytotoxicity, with an IC_{50} value of 165 μg/mL.[115]

Molecularly Imprinted Polymers

Molecularly imprinted polymers (MIPs) mimic the natural antibody-antigen mechanism to create binding sites for specific "template molecules" at the interface of cancer cell membranes or the extracellular matrix (ECM), demonstrating predetermined selectivity toward the target site.[116] The dosage of crosslinker significantly affects both the drug loading capacity and stability of MIPs.[117] In comparison to traditional bioligand modification strategies, MIPs offer enhanced stability and cost efficiency, making them promising candidates for large-scale production.[116] MIPs outperform non-imprinted polymers due to their superior selectivity and affinity. Magnetic MIPs (MMIPs), which integrate a magnetic iron core with a MIP shell, can be guided effectively using an external magnetic field to achieve targeted drug release and local magnetic hyperthermia.[118] In addition, the high specific surface area of MIONPs facilitates rapid and targeted delivery of MIPs within the organism,[119] reducing permeability issues and enhancing resistance to interference. Some scholars have designed and synthesized an MMIP using MIP technology, employing methacrylic acid (MAA) and itaconic acid (ITA) as pH-responsive monomers for efficient delivery of Zidovudine (AZT). The pH sensitivity of MMIPs was demonstrated in the treatment of BC. AZT-loaded MMIPs exhibited significantly higher cytotoxicity compared to free AZT, approximately 49 times greater, and induced apoptosis in BC cell lines by participating in the caspase-dependent apoptosis signaling pathway[120] (Figure 5).

The magnetic core preparation is identified as pivotal in MMIP synthesis. Future development of MMIP programs should prioritize optimization of the magnetic core preparation process and identification of appropriate functional monomers, templates, and cross-linking agents.

In addition to the polymers mentioned above, materials such as chitosan, Poly (methyl acrylic acid carboxyl betaine) (pCBMA), polyaniline, and others have been utilized as modifiers for MIONPs (Table 3). Polymer-encapsulated MIONPs hold significant promise in the fields of drug-targeted delivery and BC visualization imaging.

Lipids

Lipids constitute vital components of cell membranes. Biomimetic vesicle structures can be formed by phospholipid molecules, enabling the encapsulation of MIONPs and creating a natural protective barrier.
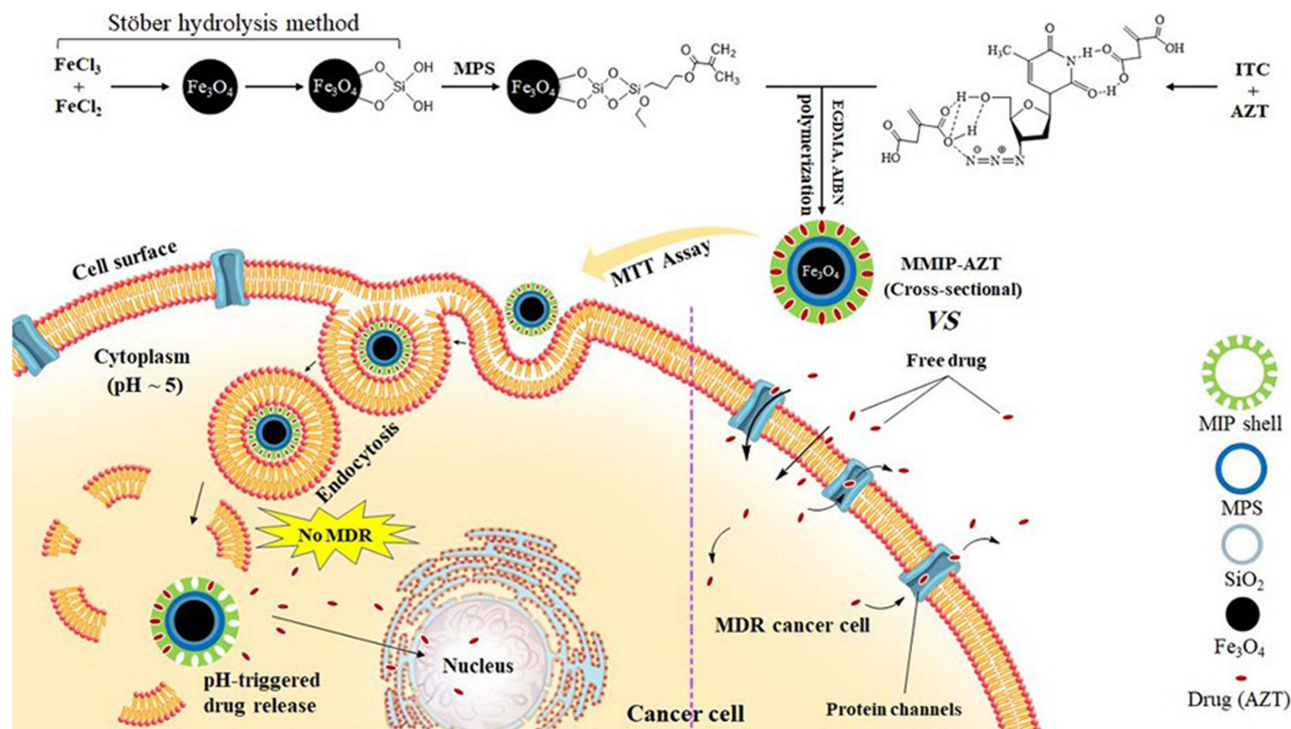
Figure 5 Schematic illustration of the synthesis of MMIOs-based MIONPs and mechanism diagram of Anti-BC. Reprinted from *Mater Sci Eng C Mater Biol Appl*. Volume 103. Hassanpour A, Irandoust M, Soleimani E, Zhaleh H. Increasing the Anticancer Activity of Azidothymidine toward the Breast Cancer via Rational Design of Magnetic Drug Carrier Based on Molecular Imprinting Technology. Page number: 109771, Copyright (2019), with permission from Elsevier.[120]

As an innovative drug delivery system, magnetic liposomes combine the dual advantages of metal nanoparticle magnetohydrodynamics and liposome technology, playing a key role in the field of targeted drug delivery: (1) Thermosensitive drug release can be achieved. Closed double-layer magnetic thermosensitive liposomes, with nano-sized iron oxide at their core, enable the modulation of drug release by altering the liposomal membrane structure at varying temperatures.[128] For instance, magnetic liposomes loaded with betulinic acid (BA), prepared via the thin layer hydration method, demonstrate increased cytotoxicity against MDA-MB-231 cells under elevated temperature conditions compared to BA alone. With a saturation magnetization intensity of 48.7 emu/g, these liposomes exhibit both thermo-sensitive drug release and superparamagnetism, making them ideal for hyperthermia-induced and remotely controlled drug delivery.[129] (2) The magnetomotive force of iron oxide is an effective strategy to achieve the fixed-point thermosensitive drug release under the action of an external magnetic field. Nanostructured lipid carriers (NLCs) incorporating MIONPs have been demonstrated to enhance the release and efficacy of chemotherapeutic agents through magnetic hyperthermia.[130] It was observed that exposure to SPIONs-NLC and MTX-SPIONs-NLC under external magnetic field stimulation increased the apoptosis rates of cancer cells from 35% (with MTX-SPIONs-NLC alone) to 50% and 65%, respectively. Moreover, cell viability demonstrated time-dependent behavior, suggesting that the enhanced cytotoxicity of MTX-loaded NLC co-formulations may be attributed to MTX release within the NLC or potentially to lipid matrix degradation. (3) External liposomes of iron oxide core were employed to enhance drug loading capacity. Development of calcium ferrite nanoparticles ($CaFe_2O_4$) for creating solid or aqueous magnetic liposomes through lipid bilayer coating or encapsulation. Solid magnetic liposomes showed superior superparamagnetic behavior, whereas aqueous magnetic liposomes exhibited approximately 10% higher drug encapsulation efficiency (EE%) compared to solid counterparts. These findings underscore the promising magnetic properties and high EE% of drug-loaded nano-carriers containing biocompatible calcium ferrite nanoparticles, suggesting their potential for dual therapy combining chemotherapy and magnetic hyperthermia in BC treatment.[131] (4) The flexibility of the lipid bilayer allows the incorporation of a PEG "stealth layer" to increase blood circulation time, making it an excellent candidate material for contrast agents.[132] Magnetic liposomes are engineered to form nanoclusters in a controlled manner, typically resulting in

Table 3 Review of MIONPs Based on Different Polymer Coatings as a Platform for BC Diagnosis and Treatment

MIONPs	Synthesis Method	Physical Property	Protective Layer	Loaded Drugs	Machine	Literature
Fe_3O_4@PCBMA	pyrolysis	Zeta potential: −9 mV	pCBMA	Simvastatin	Inhibition of HMGCR expression leads to down-regulation of the mevalonate (MVA) pathway and glutathione peroxidase 4 (GPX4), producing more LPO to induce iron death in cancer cells	[121]
Pani/γ-Fe_2O_3NPs	Coprecipitation	Size:37.87±6.48 nm Zeta potential: 24.81 ± 0.38 mV	Polyaniline	N/A	Acts on tumor-associated macrophages (TAMs) and induces the transformation of M2 macrophages to M1 macrophages to inhibit tumor growth	[122]
BSA/p(APTMACl)@ALG/Fe_3O_4	Coprecipitation	Size:105nm Zeta potential: −42mV	Poly ((3-acrylamidopropyl) trimethyl ammonium chloride) (p(APTMACl))	Curcumin	Inhibition of TNBC cell proliferation metastasis and epithelial-mesenchymal transition (EMT) affects TNBC cell invasive metastasis by regulating the Hedgehog/Gli1 pathway	[123]
LUT-CS/Alg-Fe_3O_4-NPs	Pre-gelation and co-precipitation	Size:30–120nm Zeta potential: −13.3 ± 1.6mV	Chitosan and Alginate	Lutein	Inhibits tumor vascular proliferation and cell proliferation by decreasing the expression of inflammatory factors and increasing superoxide dismutase for antioxidant purposes	[124]
Fe_3O_4@CS-Agarose/Pd	Ultrasound-assisted synthesis	Size:10nm	Chitosan-agarose	Pd	Properties Eliminate free radicals to inhibit DNA and RNA mutations and reduce the proliferation of cancer cells	[125]
LIONs	Coprecipitation	Size: 111.85 ± 3.75 nm Zeta potential: −13.6 mV	Lignin	Methotrexate	Enhances caspase-3 activity and lowers glutathione levels	[126]
Fe_3O_4 @PDA/GOx NPs	N/A	N/A	Polydopamine (PDA)	Glucose oxidase	Generation of ROS to induce apoptosis in cancer cells	[127]

heightened local magnetic field inhomogeneity, prolonged water residence time, and increased spin-spin relaxation rate (r_2 or $1/T_2$ description) of protons in the environment. This approach facilitates achieving an optimal r_2/r_1 ratio,[133] enhancing the intensity of dark contrast signals in T_2-weighted MRI.

In addition to the synthetic phospholipids used above, another type that can be included in the scope of magnetic liposomes is bionic MIONPs. This approach offers an opportunity to merge the characteristics of natural cell membranes with those of artificial iron oxide core materials. This bionic phospholipid membrane replicates the physiological composition and motility of normal cells, enabling successful evasion of non-specific RES uptake and offering significant advantages in the realm of targeted delivery using MIONPs. For example, recent research utilized a magnetic core modified with extracellular vesicles (EVs)[134,135] extracted from BC cells and employed MPI to monitor and characterize brain metastasis in BC. This study demonstrated that EV-modified MIONPs can traverse the blood-brain barrier (BBB), serving as both an imaging tool and a drug delivery carrier for targeted brain metastasis. With the cancer cell membrane (CM) as a shelter of polyethylene imine bionic magnetic nano gel (NG) system can effectively achieve (DTX) and antibody (CD47 siRNA) homologous targeted delivery[136] (Figure 6). By downregulating the "don't eat me" signal of cancer cells, it induced immunogenic cell death (ICD) and promoted macrophage M1 polarization, while reversing the immunosuppressive microenvironment[137] caused by immune checkpoint inhibition, promoting dendritic cell (DCs)
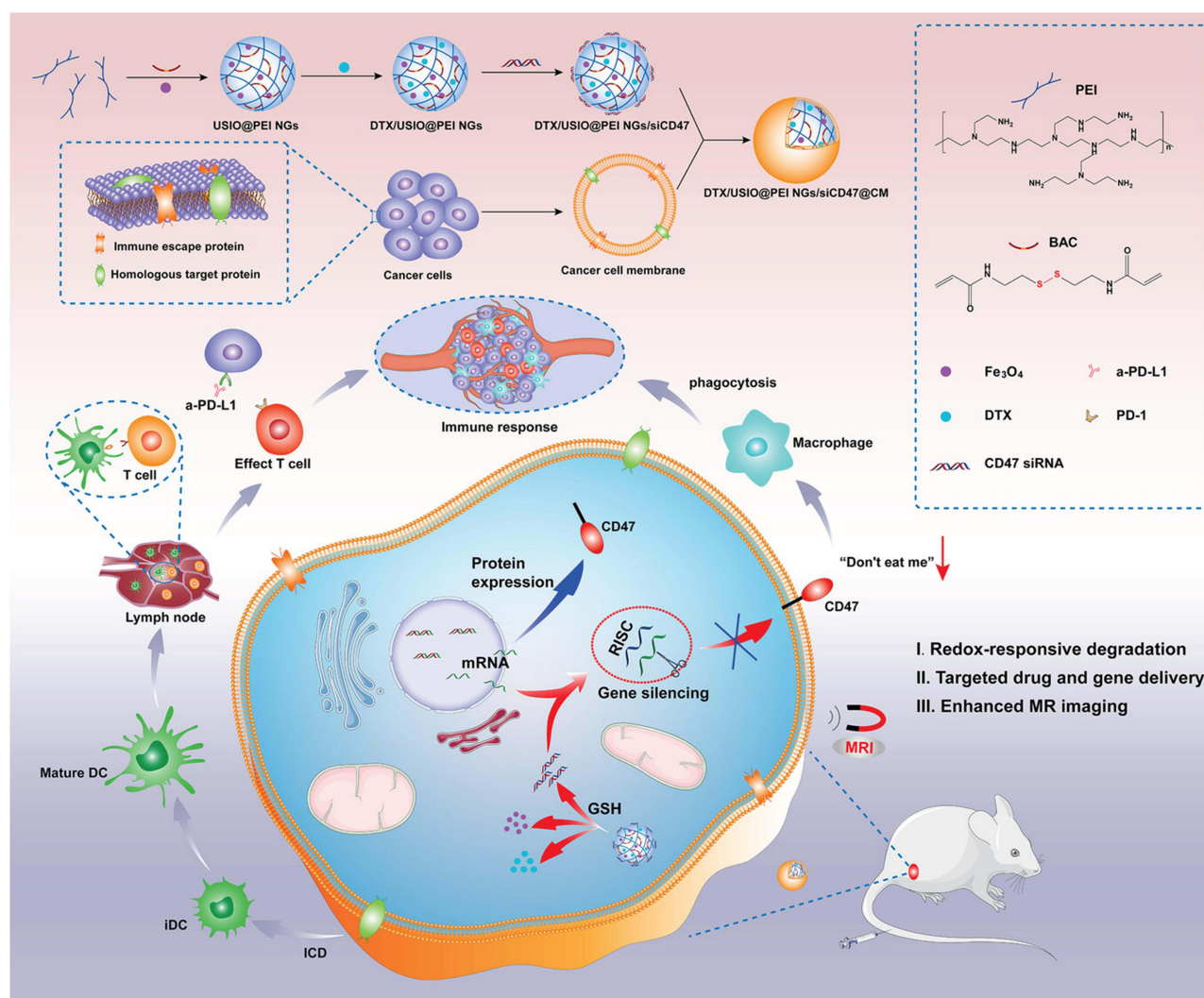

Figure 6 Schematic illustration of the synthesis of DTX/USIO@PEI NGs/siCD47@CM for synergistic chemo-immunotherapy and MRI of tumors in vivo. Reprinted from Li L, Gao Y, Zhang Y, et al. A Biomimetic Nanogel System Restores Macrophage Phagocytosis for Magnetic Resonance Imaging-Guided Synergistic Chemoimmunotherapy of Breast Cancer. *Adv Healthc Mater.* 2023;12 (26): e2300967. © 2023 Wiley-VCH GmbH.[136]

maturation and cytotoxic T lymphocytes (CTLs) infiltration into tumor sites, and effectively inhibiting the growth and lung metastasis of primary BC.

Due to the intricate nature of the tumor microenvironment, hybrid bio-mimetic membranes coated with a combination of two or more cell membranes exhibit superior tumor-targeting efficiency compared to pure bio-mimetic membranes.[138] A hybrid biomimetic membrane, modified with osteoclasts and tumor cells, is effectively targeted towards osteoclasts and tumor cells at bone metastasis sites via a homologous targeting mechanism. This approach is complemented by sonodynamic therapy and chemodynamic therapy to mitigate malignant bone metastasis in BC. Nevertheless, mere biofilm modification proves insufficient. Excessive use of immune cell membrane-coated MIONPs may induce or exacerbate inflammation through interactions with the immune system, resulting in the release of pathological mediators. Hence, the development of more intelligent and effective biofilm-coated MIONPs is imperative to facilitate potential industrial production and clinical translation.

Proteins and Amino Acids

In comparison to polymers, lipids, and other materials, protein/amino acids-based nanocarriers exhibit superior biofunctionality, biomolecular recognition ability, and renewable sourcing potential.

Proteins play a crucial role in gene delivery due to their distinct advantages. Traditional gene therapy methods often rely on retroviruses or adenoviruses, which inherently possess toxicity and induce immunogenic responses upon frequent or prolonged administration. Protein-based nanocarriers, utilizing proteins closely resembling natural proteins as shells, address the drawbacks of viral systems and serve as alternatives to viral vectors in gene therapy. Furthermore, protein-coated MIONPs are straightforward to prepare and scale up in production. A polyethyleneimine (PEI)-sericin-modified MIONPs have been reported for delivering siRNA to the tumor site, demonstrating the positive effect of tyrosine kinase-like orphan receptor (ROR1) gene downregulation on TNBC treatment in both in vivo and in vitro experiments.[139] The surface cationic properties of PEI enhance particle stability and promote effective transfection of ROR1 siRNA. Sericin, on the other hand, mitigates the binding of NPs to plasma proteins, thereby reducing their inflammatory potential compared to other commonly used biodegradable polymers.[140] Another study involves SPIONPs (SP-AH) coupled with Argonaute 2 protein and anti-HER2 antibody as carriers of autophagy-inhibiting microRNA (MIR376B), which effectively downregulates autophagy-related targets of miRNA and inhibits autophagy activity in BC cells, representing a novel adjuvant therapeutic agent for BC.[141] In addition to serving as drug delivery carriers, protein coatings are also considered for the fabrication of high-performance MIONPs T_2 CAs, such as casein,[142] known for their high permeability, proton affinity, and plentiful hydrated groups. The T_2 relaxation time of MIONPs coated with casein is 2–3 times longer than that of MIONPs coated with amphiphilic polymers.

Amino acid-coated MIONPs are mostly used as carriers for chemotherapeutic drugs. For example, lysine-coated MIONPs loaded with tamoxifen (TMX), the data showed that the apoptosis induced by F-Lys-TMX NPs treatment for 48 and 72 h (53.1% and 58.6%, respectively) was significantly higher than that induced by free TMX treatment for 48 and 72 h (36.1% and 45.7%, respectively), and the apoptosis induced by HER2 in F-Lys-TMX NPs treatment significantly reduced the expression levels in cells.[143] Another interesting feature of amino acid carriers is their diversity of functional groups, which allows for the coupling of targeted ligands or drug molecules.[12] The NPs are also characterized by a variety of functional groups. In addition, the tumor acidic microenvironment facilitates the cleavage release of the affixed drug, suggesting that amino acid-based MIONPs have a better chance of targeting the drug to the tumor site. When glutamic acid is in-situ encapsulated on the surface of iron oxide magnetic nanoparticles, high density of amine and carboxyl functional groups of glutamic acid provide abundant coupling sites for drug molecules. The DOX and MTX dual drug coupling exhibits the potential to track and kill cancer cells under pH-dependent release and thermal activation of external AC magnetic field.[144]

MIONPs based on proteins or amino acids also present certain limitations:[145] Firstly, natural proteins vary widely in molecular weight. This variability can impact the particle size distribution of MIONPs during industrial production across different protein batches. The advent of recombinant protein technology[146] is expected to effectively mitigate this challenge. Compared to natural proteins, recombinant proteins offer consistent batch-to-batch performance, abundant availability, and the capability to be engineered for specific properties such as solubility, stability, and efficacy. Secondly,

certain proteins or amino acids can be prone to degradation because of their natural hydrophilicity, which hinders controlled drug release. The use of chemical cross-linkers to enhance controlled release poses the risk that incompletely reacted cross-linkers may persist within MIONPs. This persistence could hinder biodegradation or lead to the formation of toxic byproducts during circulation in organisms. Therefore, exploring novel non-toxic and degradable cross-linkers is crucial for mitigating these issues.

Inorganic Nanomaterials
Silicon Dioxide (SiO$_2$)

Silica is widely regarded as one of the most ideal coatings for MIONPs due to several advantages. Firstly, it offers excellent stability in tumor acidic microenvironment. When administered intravenously under physiological conditions, bare iron oxide nanoparticles release iron ions that accumulate in the liver. This iron ions overload increases ROS, causing oxidative stress that damages mitochondria, induces protein denaturation, and accelerate damage to cell membranes and DNA.[147] Silica coating serves as an ionic surface modifier, reducing cytotoxicity by enhancing spatial repulsion between particles and preventing aggregation. Secondly, mesoporous silica structure significantly enhances drug loading. For instance, the Co-loading of two different drugs, letrozole and curcumin, was achieved by coating the magnetic NiCoFe$_2$O$_4$ core with a thin layer of silica and niosomal structure. The niosomal structure confers pH responsiveness, while silica provides a high loading capacity.[148] Thirdly, the physical properties of silica coating can be precisely controlled by adjusting reaction conditions, allowing for modulation of the surface roughness of MIONPs. This enhancement improves their capability to bind to biological molecules and increases sensitivity to electron radiation, potentially augmenting the effectiveness of radiotherapy (RT).[149] For example, the near-infrared light and magnetic field dual-effect anticancer drug PSiNPs@(Fe$_3$O$_4$/Au) showed certain advantages in the treatment of multidrug resistance in BC,[150] achieving a synergistic "magnetothermal + photothermal" anti-tumor enhancement effect. Another notable study involves integrating plasma AuNPs and silica-coated iron oxide NPs (Fe$_3$O$_4$/SiO$_2$NPs) as magnetically aligned components within a temperature and pH dual-responsive polyvinyl alcohol (PVA) gel network. This preparation exploits the swelling and collapse of the PVA gel and the plasma-induced heating of AuNPs to facilitate the capture and release of the highly selective cytotoxic anticancer agent DOX in targeted tissues. Experiments indicate that compared to the control group, Au/Fe$_3$O$_4$/PVA-10%DOX achieves a tumor inhibition rate of (70±6.3%) under near-infrared light irradiation and magnetic field exposure.[151] Even though external magnetic fields can accelerate the aggregation of mesoporous silica-MIONPs at tumor sites, they still lack specific localization functions. The abundant silanol groups on the silica surface provide ideal anchor points for the covalent bonding of specific ligands. For example, the modification of mesoporous silica-coated superparamagnetic Fe$_3$O$_4$ nanoparticles (HA-MSNs) with hyaluronic acid (HA) effectively addresses these localization function shortcomings.[152] HA is chemically or physically cross-linked with functionalized nanoparticles through covalent bonds or non-covalent means. This modification enables targeted inhibition of tumor infiltration and metastasis through cell surface receptors such as CD44 and RHAMM.[153] Furthermore, HA imparts intrinsic anti-inflammatory properties[154] and reshapes the ECM, which is the key to regulating the immune system and cancer monitoring.

Gold

Gold coating will induce surface plasmon resonance to generate local heat flow under the stimulation of light. Unlike chemotherapy,[155] gold-coated Fe$_3$O$_4$ composite nanoparticles can reshape the tumor microenvironment by mediating a photothermal effect that reduces cancer-associated fibroblasts (CAF).[156] Additionally, they enable photothermal-controlled rapid drug release and targeted recognition in vitro.

A comprehensive diagnostic and therapeutic technique based on gold-coated MIONPs for photoacoustic/MRI dual model imaging diagnosis and photothermal therapy[157] offers the advantages of short-term repeatable treatment, safety, and low drug resistance. A magnetic-optical iron-gold core-shell nanoparticle with a distinct Raman reporting factor can serve as a four-color surface-enhanced Raman scattering (SERS) nanolabel to quantitatively identify and detect four surface protein markers on individual tumor cells in whole blood simultaneously, providing a means for detecting and monitoring cancer metastasis.[158] Other researchers have designed a magnetically targeted ^{198}Au radionuclide therapeutic

drug designed to target HER2-positive BC by coupling with the biomacromolecule trastuzumab (Tmab).[159] Combining magnetic hyperthermia with radionuclide therapy can enhance blood flow in tumors and induce the generation of ROS that damage DNA under ionizing radiation. This $Fe_3O_4@^{198}Au$-Tmab radioactive bioconjugate enables a multimodal platform for combined ionizing radiation and magnetic hyperthermia treatment. It has been observed in studies that gold coating also induces the expression of HSP70. Elevated levels of this immunogenic protein can enhance immune cell recognition of tumor cells and promote ICD.[160] The gold coating can effectively improve the efficiency of photothermal conversion and cooperate with MRI for accurate tumor detection and monitoring treatment. Compared with other metals (copper and silver), the drawback of gold coating is its high cost, which limits its suitability for industrial production.

Graphene Oxide

Graphite interacts with strong oxidizing agents to produce graphene oxide (GO), which contains oxygen-containing functional groups such as -OH, -COOH, and epoxy groups on its surface. These groups are responsible for the hydrophilicity and efficient drug-loading capacity of GO.[161] The GO-Fe_3O_4 hybrid nanoparticles can be synthesized by interacting GO with the surface amino groups of MIONPs coated with short-chain amino acids. The synthesis of non-covalent (nc-GO-Fe_3O_4-HCPT) based on the physical adsorption of Hydroxycamptothecin (HCPT) on the surface of GO-Fe_3O_4 nanocomposites based on π-π interactions possessed more potent antitumor activity than the covalent (c-GO-Fe_3O_4-HCPT) synthesized based on the chemical binding of modified HCPT to GO-Fe_3O_4. The superiority of nc-GO-Fe_3O_4-HCPT over c-GO-Fe_3O_4-HCPT in NRU analysis was evidenced by a more pronounced reduction in mitochondrial activity.[162] Another gefitinib-loaded GO exhibited 64% drug-carrying capacity through nanocomplexes formed by covalently linking with amine-functionalized iron oxide nanoparticles, and at a concentration of 40 ppm, GOIGF had an incremental inhibitory potential of ~10% over pure GF.[163] The good electrical and thermal conductivity of GO synergistically enhanced the specific absorption rate (SAR).[164] For instance, it was developed that tumor-targeted magnetic nanoparticles (FVIOs-GO-CREKAMTD) with a high SAR and enhanced ROS generation. The combination of MIONPs-mediated magnetothermal dynamics (MTD) and ROS-mediated ICD demonstrated that reducing the exposure time to low doses of alternating magnetic fields could achieve comparable anti-tumor efficacy as conventional magnetothermal therapy. Furthermore, this approach promoted the infiltration of CD4 helper proteins and CD8 cytotoxic T lymphocytes into tumors.[165] Additionally, the size of MIONPs significantly influenced GO performance, where smaller MIONPs enhanced GO surface reactivity and exhibited superparamagnetic behavior. Moreover, their pharmacokinetics, stability, and toxicity characteristics were also affected.[166] These size-dependent changes in application performance highlight the importance of selecting appropriate GO-MIONPs conjugates in biomedical fields such as MRI.

Metal Oxides/Metal Sulphide

Metal oxides/metal sulfides have emerged as highly promising candidates in the field of MIONPs-related bionanomedicine owing to their distinctive physicochemical properties.

Nanoscale metal oxides, such as MgO, NiO, CdO, and ZnO, have found extensive applications in antibacterial and anticancer research due to their substantial pore volume, non-toxic nature, cost-effectiveness, exceptional thermal stability, and chemical durability. The underlying mechanisms encompass but are not limited to DNA chain disruption in cancer cells,[167] cell wall damage[168] and regulation of cellular oxidative homeostasis.[169] Four novel high-purity α-Fe_2O_3-ZnO nanostructures were synthesized (including disk-shaped (FZ-ND), spindle-shaped (FZ-NSP), rod-shaped (FZ-NR) and spherical (FZ-NS) structures) by simple solvothermal method combined with heat treatment. Among these nanostructures, the FZ-NSP sample exhibited the highest cytotoxicity to MCF- cells at all concentrations, showing a concentration-dependent effect, reaching 80% at a concentration of 250 μg/mL.[170] Transition metal chalcogenides (TMDs), particularly those operating within the near-infrared window (NIR-II), are promising candidates in the field of photoacoustic (PA) imaging. These materials can enhance PA/MR imaging when combined with MIONPs. Moreover, they have the potential to trigger ICD, which can reverse immunosuppression and enhance the therapeutic efficacy against primary, distant, and metastatic tumors.[171] This dual capability makes TMDs valuable for advancing diagnostic and therapeutic strategies in BC.

It is noteworthy that, in comparison to the protein corona formed on the surface of PEG-MIONPs, the sulfide coating demonstrates a reduction in protein corona formation on the surface of MIONPs. Moreover, the protein corona specifically adsorbed on the sulfide-coated MIONPs exhibits a decreased likelihood of participating in nanoparticle-targeted transport and immune response mediation, while also displaying enhanced resistance to phagocytosis by macrophages, resulting in an extended in vivo circulation time.[69]

Summary and Outlook

In recent decades of clinical research on BC, significant efforts in optimizing the structure of MIONPs have primarily aimed to enhance their effectiveness as excellent T_2 contrast agents (T_2CAs). However, the defects of MIONPs as T_2CAs have been gradually exposed in the process of clinical practice: (1) As a negative contrast agent, the dark signal generated by MIONPs can be easily confused with signals from hematoma, calcification, air, and other phenomena within the body. (2) Their high magnetic moment can induce magnetization artifacts known as the "halo effect", distorting the background around lesion tissues. (3) Larger MIONPs exhibit slow clearance from the body, potentially leading to cumulative toxicity with prolonged use. In recent years, increasing attention has been directed toward engineering the crystal structure of MIONPs to enhance their T_1 relaxivity and develop T_1 contrast agents (T_1CAs) based on MIONPs. In recent studies, iron oxide nanoparticles ranging from 1.9 to 4.9 nm in size have been synthesized, with 3.6 nm identified as optimal for serving as T_1-weighted MRI CAs.[70] In addition, some experiments compared different coatings, synthesis methods, and dopants to improve the T_1 contrast enhancement of MIONPs. Despite numerous demonstrations of their potential as T_1-weighted CAs, the complexity of parameter control has hindered the clinical validation of suitable MIONPs. Moreover, the ultra-small particle size may lead to heightened surface energy within the body, potentially resulting in aggregation, and these potential risks and challenges will increase in proportion with the scale of production.

To address these challenges, there is growing interest in T_1/T_2 dual-mode CAs.[172] For instance, DNA was utilized as a precisely controllable and stable ligand to assemble dimeric ultra-small magnetic nanoparticles. Under ultra-high field MRI, DMA exhibits moderate local magnetic field homogeneity while maintaining superparamagnetic behavior, with an r_2/r_1 value of approximately 5.93, falling within the ideal range for T_1/T_2 dual-mode contrast agents ($5 < r_2/r_1 < 10$). DMA exhibits excellent dual-mode imaging output, filtering out magnetization artifacts with high spatial resolution under ultra-high magnetic fields. Furthermore, a model representing various stages of hematoma development adjacent to the tumor assesses DMA's in vivo MR precision imaging for BC, highlighting its accurate tumor recognition. Subsequent toxicological analysis confirms DMA's excellent biosafety profile in vivo. The established principles of surface modification effects on T_1 and T_2 remain pertinent for T_1/T_2 dual-functional contrast agents, emphasizing attributes like high hydrophilicity, optimal bioavailability, and stable surface coatings. However, further extensive research is necessary to fully assess the advantages of dual-mode imaging methodologies in models that closely mimic clinical conditions relevant to breast cancer. Despite the fact that 2D/3D models have demonstrated good BC diagnosis and treatment results by using MIONPs-based drug delivery systems, achieving clinical translation remains the biggest existing challenge for MIONPs. In fact, we still lack in vitro/in vivo models that summarize the detailed characteristics of BC itself and the complex microenvironment, and most studies rely on animal models, where inter-species differences inevitably affect researchers' judgment of whether drugs with good pharmacokinetic performance in animal models will produce the expected results if applied in humans. In recent years, new progress has been made in the in vitro humanization model of BC, and the emerging cutting-edge technology of "organoid/organ chip/microfluidic organ chip technology" can simulate and reproduce the microenvironment of the human body under actual physiological and pathological conditions. This new frontier technology can simulate and reproduce the microenvironment of the human body under actual physiological and pathological conditions, which can be helpful for the preclinical research of surface-engineered MIONPs as well as for the promotion of clinical research.

Surface modifications of MIONPs have all been developed to reduce the challenges of traditional drug delivery systems. The ideal surface-engineered MIONPs function as a multifunctional vehicle, ensuring precise release and retention of therapeutic agents at the appropriate dosage, location, and timing to maximize efficacy while minimizing side effects. Furthermore, surface-engineered MIONPs offer enhanced contrast, sensitivity, and spatial resolution for clinical imaging modalities such as MRI and PA imaging, as mentioned earlier. With the advancement of

environmentally friendly and intelligent surface-engineered MIONPs for targeted drug delivery systems, there will be groundbreaking developments in the diagnosis and treatment of BC. The emergence of organoid models as a novel platform signals an increasing role for MIONPs in cutting-edge clinical solutions.

Abbreviations

MIONPs, Magnetic iron oxide nanoparticles; IARC, International Agency for Research on Cancer; BC, Breast Cancer; MRI, Magnetic Resonance Imaging; TNBC, Triple Negative Breast Cancer; RES, Reticuloendothelial System; CAs, Contrast Agents; SPIO, Small particles of iron oxide; USPIO, Ultrasmall particles of iron oxide; SPIONs, Superparamagnetic Iron Oxide Nanoparticles; Tc99, Technetium-99m; BD, Blue Dye; SLN, Sentinel Lymph Node; MT, MagTrace®; FM, Ferumoxytol®; SUH, Sahlgrenska University Hospital; FAHNMU, The First Affiliated Hospital with Nanjing Medical University; CTC, Circulating Tumor Clusters; MPI, Magnetic Particle Imaging; FMI, Fluorescence Molecular Imaging; NIRF, Near-infrared Fluorescence; AMF, Alternating Magnetic Field (AMF); MHT, Magnetic Hyperthermia; EPR, Enhanced Permeability and Retention; ROS, Reactive Oxygen Species; FT, Ferroptosis Therapy; LPO, Lipid Peroxides; VTPA, Virus Spike Tumor-activated Hyperthermia Agent; PU, Polyurethane; DOX, Doxorubicin; PEG, Polyethylene Glycol; VEGF, Vascular Endothelial Growth Factor; RES, Reticuloendothelial System; pHLIP, pH low insertion peptide; MPS, Mononuclear Phagocyte System; ABC, accelerated blood clearance; MIPs, Molecularly Imprinted Polymers; ECM, Extracellular Matrix; MAA, methacrylic acid; ITA, Itaconic Acid; AZT, Zidovudine; pCBMA, poly (Carboxybetaine Methacrylate); MVA, mevalonate; GPX4, Glutathione Peroxidase 4; TAMs, Tumor-associated Macrophages; EMT, Epithelial-mesenchymal Transition; BA, Betulinic Acid; GT, Gene Therapy; PTT, Photothermal Therapy; BA, Betulinic Acid; EVs, Extracellular Vesicles; BBB, Blood-brain Barrier; NG, nanogel; NLC, Nanostructured Lipid Carriers; TMX, Tamoxifen; CAF, Cancer-associated Fibroblasts; ICD, Immunogenic Cell Death; DCs, Dendritic Cells; CTLs, Cytotoxic T Lymphocytes; PEI, Polyethyleneimine; TMX, tamoxifen; HA, Hyaluronic Acid; SERS, Surface Enhanced Raman Scattering; GO, Graphene Oxide; HCPT, Hydroxycamptothecin; TMDs, Transition Metal Chalcogenides; MTD, Magnetothermal Dynamics;; ECM, Extracellular Matrix; ITA, Itaconic Acid.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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