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Review

Ferroptosis-based nano delivery systems targeted therapy for colorectal cancer: Insights and future perspectives

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ABSTRACT

There are limited options for patients who develop liver metastasis from colorectal cancer (CRC), the leading cause of cancer-related mortality worldwide. Emerging evidence has provided insights into iron deficiency and excess in CRC. Ferroptosis is an iron-dependent form of programmed cell death characterized by aberrant iron and lipid metabolism, which play crucial roles in tumorigenesis, tumor progression, and treatment options. A better understanding of the underlying molecular mechanism of ferroptosis has shed light on the current findings of ferroptosis-based nanodrug targeting strategies, such as driving ferroptosis in tumor cells and the tumor microenvironment, emerging combination therapy and against multidrug resistance. Furthermore, this review highlights the challenge and perspective of a ferroptosis-driven nanodrug delivery system for CRC-targeted therapy.

1. Introduction

Colorectal cancer (CRC) is an aggressive malignancy, with more than 50% of patients developing liver metastases [1]. Its genomic instability and inflammatory tumor microenvironment (TME) result in a lack of response to current therapies such as chemotherapy (5-fluorouracil, oxaliplatin, or irinotecan) and targeted therapies (bevacizumab targeting vascular endothelial growth factor or cetuximab targeting epidermal growth factor receptor), radiotherapy and immunotherapy [2]. Therefore, there remains an urgent need for effective treatment strategies to extend the life expectancy of end-stage CRC patients.

Ferroptosis, a recently discovered form of regulated cell death, is biochemically, genetically, and morphologically distinct from apoptosis, autophagy, and necrosis [3]. It features the alteration of mitochondria, aberrant accumulation of reactive oxygen species (ROS), and peroxidation to lethal levels in cell membranes. Proposed in 2012, researchers extensively studied ferroptosis due to its engagement in cellular metabolism, immunity, aging, and the progression of multiple diseases [4]. The complex biological processes of ferroptosis are caused by an imbalance between iron, lipid dynamics, and intracellular antioxidant systems. A marker of ferroptosis is the demand for iron. When iron chelators reversed erastin-induced lethality, it revealed that iron was initially involved in ferroptosis [4]. The

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ability of iron to gain or lose electrons quickly allows it to transform H_2O_2 into toxic ROS via the Fenton reaction. Polyunsaturated fatty acids (PUFAs) are one of the main targets of lipid peroxidation [5]. Excess ROS results in a build-up of toxic lipid peroxidation products, including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), causing membrane damage due to oxidation of PUFAs. The upregulated expression of acyl-CoA synthetase long-chain family member 4 (ACSL4) is also considered a specific biomarker and driving factor to provoke ferroptosis owing to its capability to enrich the PUFAs content of phospholipids. PUFAs-containing phosphatidylethanolamines (PE), especially those containing arachidonic acid (AA) and adrenaline (AdA), are most susceptible to lipid peroxidation that triggers ferroptosis. Next, AA-PE and Ada-PE are catalyzed into the toxic peroxidation products AA-PE-OOH and AdA-PE-OOH by lipoxygenases (LOX). At the same time, accumulating these lipid peroxides may disrupt lipid bilayer properties and generate cytotoxic reactive fragments [3]. Meanwhile, there are several defense pathways against ferroptosis in cells, of which the most prominent is mediated by glutathione peroxidase 4 (GPX4), which inhibits ferroptosis by specifically catalyzing lipid peroxidation through glutathione (GSH) [6]. Inhibiting system Xc^- (a cystine/glutamate antiporter system), consisting of suppressing solute carrier 7A11 (SLC7A11) and suppressing solute carrier 3A2 (SLC3A2), could reduce GSH levels and GPX4 activity, causing excessive accumulation of ROS. In addition, the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2/Nrf2) signaling pathway corrects redox imbalance and improves cellular defense against ferroptosis by enhancing the upregulation of various cellular antioxidant genes (e.g., HO-1, NADPH, SLC7A11). Ferroptosis suppressor protein 1 (FSP1) is also shown to act as a potent ferroptosis inhibitor capable of catalyzing the regeneration of CoQ10 to produce ubiquinol from NAD(P)H to inhibit lipid peroxidation reactions [7]. With further research, the potent endogenous antioxidant tetrahydrobiopterin/dihydrobiopterin (BH4/BH2) produced by guanosine-triphosphate-cyclohydrolase-1 (GCH1) can also remodel lipids and thus prevent uncontrolled lipid peroxidation. When the biological activity of these defense systems is reduced, iron-dependent lipid peroxidation promotes cell death by disrupting mitochondria, cellular membrane structures, and lipoproteins, which is not dependent upon the kinase activities of the caspase family [8] (Fig. 1).

As a unique mechanism of cell death, ferroptosis may offer new therapeutic opportunities for treating cancer resistant to traditional therapies. Conversely, tumor progression and drug resistance are usually characterized by properties such as the polarization of malignant cells to a mesenchymal or poorly differentiated state, which is more vulnerable to ferroptosis-inducing agents [9,10]. On the other hand, cancer cells show less resistance to ferroptosis due to their specific mutations and elevated levels of oxidative stress. In addition, the immune system may protect against tumorigenesis partly through ferroptosis, in which tumor cells are sensitized to ferroptosis by $CD8^+T$ cells through interferon-γ (IFN-γ) [11].

Some clinical medications have been successfully applied to lyse tumor cells by inducing ferroptosis, including

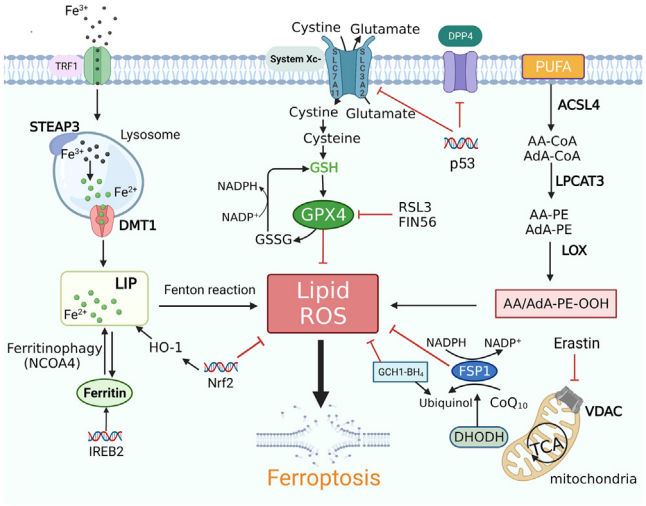

Fig. 1 – Schematic illustration of the occurrence and regulation of ferroptosis. Abbreviations; TFR1: transferrin receptor 1; DMT1: divalent metal transporter 1; DPP4: dipeptidyl peptidase-4 STEAP3: six-transmembrane epithelial antigen of prostate; LIP: labile iron pool; PUFA: polyunsaturated fatty acids; ACSL4: acyl-CoA synthetase long-chain family member 4; AA: arachidonic acid; AdA: adrenic acid; LPCAT3: lysophosphatidylcholine acyltransferase 3; LOX: lipoxygenases; Xc^-: cystine-glutamate exchange system; HO-1: heme oxygenase-1; FSP1: ferroptosis suppressor protein 1; GCH1: GTP cyclase hydrolase-1; DHODH: dihydroorotate dehydrogenase; VDAC: voltage dependent anion channels.

breast cancer, drug-resistant gastrointestinal tumors, and neuroblastoma [12–14] (Table 1). As high-throughput screening technology matures, small molecule inducers and biomolecules related to the regulation of ferroptosis have been explored to target ferroptosis pathways and show marked effects in various cell lines, which are expected to revolutionize cancer treatment. However, improving the selectivity of these ferroptosis inducers to avoid unnecessary side effects is an urgent challenge for clinical translation. It is worth noting that nanotechnology provides new possibilities for triggering ferroptosis in cancer treatment. With the unique physicochemical properties of nanomaterials, nanodrug delivery systems (nano-DDSs) can not only enhance drug solubility and improve drug circulation time *in vivo* but also achieve targeted delivery and controllable release of drugs [15]. First, this review presents the current status and regulatory mechanisms of ferroptosis-related studies in CRC treatment. Next, we systematically gain insight into the recent advances in multiple types of nano-DDSs in treating CRC.

2. Current status of ferroptosis studies in CRC

Despite substantial advances in CRC treatment over the years, drug resistance and metastasis triggered by evasion of apoptosis and anti-apoptosis enhancement still pose

Table 1 – Clinical drugs and experimental compounds have been proven to induce ferroptosis in tumor cells.

Drug name	Mechanism	Cancer	Refs.
Sorafenib	Inhibits the absorption of cystine by system Xc^-, causes GSH depletion; activates NRF2 against ferroptosis	Hepatocellular carcinoma	[101,102]
Artemisinin compounds Dihydroartemisinin/Artesunate	Sensitizes cells to ferroptosis through the regulation of iron homeostasis	Colorectal cancer	[103]
Cisplatin	Increases GSH consumption and GPX deactivation	Pancreatic ductal adeno-carcinoma	[16]
Simvastatin	Downregulates the mevalonate pathway and GPX4	Triple-negative breast cancer	[104]
Buthionine Sulfoximine	Impedes GSH synthesis as the γ-glutamylcysteine synthetase inhibitor	Clear cell renal cell carcinoma	[105]
Sulfasalazine	Inhibits the absorption of cystine by system Xc^-, causes GSH depletion	Ovarian/Breast cancer	[106,107]
Siramesine and lapatinib	Reduces the expression of iron transport proteins and ferritin and enhances the expression of transferrin	Breast cancer	[108]
Erastin	Prevents cystine import and causes GSH depletion	Triple-negative breast cancer	[109]
Doxorubicin	Induces iron overload by affecting iron	Colorectal/Liver cancer	[59]
Vitamin C	Induces ferritinophagy and subsequent degradation of ferritin	Anaplastic thyroid cancer	[110]

enormous challenges. Growing evidence suggests that ferroptosis may be an alternative strategy against tumor cells that are insensitive to conventional chemotherapy (Table 2). For example, the results indicated that cisplatin might show more significant cytotoxicity in HCT116 cells by reducing GSH levels and GPX4 activity and increasing the susceptibility of tumor cells to erastin [16]. The therapeutic effect of the EGFR-targeted drug cetuximab is still severely limited by the 50% RAS mutation rate of metastatic CRC [17]. Ye et al. demonstrated that cetuximab promotes RSL3-induced ferroptosis in KRAS-mutant CRC cells by inhibiting Nrf2/HO-1 pathway activation based on western blotting and immunohistochemistry assays [18]. Similarly, significant GSH depletion and lipid peroxidation were observed in KRAS mutant HCT116 and LoVo cells and inhibited the migration of mutant CRC cells by reducing epithelial-mesenchymal transition (EMT) when combined treatment with β-elemene and cetuximab [19]. In addition, in the latest reports, several ferroptosis-related genes (Table 3) are available as biomarkers to predict the diagnosis and prognosis of CRC patients, which suggests that ferroptosis is associated with the progression of CRC to a certain extent.

GPX4 is the link between GSH metabolism and lipid peroxidation associated with iron metabolism. Researchers analyzed GPX4 expression and its impact on cancer patient survival through public databases. They found that GPX4 is highly expressed in CRC through epigenetic regulation and negatively correlated with patients' overall survival and disease-free survival [20]. Tian et al. discovered that RSL3 could induce ferroptosis in a time-dependent and dose-dependent manner in CRC cells (HCT116, HT29, and LoVo), and the intracellular ROS levels and transferrin expression increased, accompanied by reduced GPX4 [21]. The proto-oncogene SRSF9 is highly expressed in colon cancer [22]. Knockdown of SRSF9 by specific shRNAs enhanced erastin-induced ferroptosis in LoVo and SW480 cells, as evidenced by a significant increase in MDA levels in the cells and a significant inhibition of GPX4 expression [23].

In contrast, overexpression of SRSF9 by gene transfection enhanced the resistance of Caco2 and DLD1 cells to erastin-induced ferroptosis. The same result was observed in a tumor-bearing mouse model, where knockdown of SRSF9 enhanced the tumor growth inhibitory effect of erastin by downregulating GPX4 expression. In addition, He et al. explored the role of microRNA-15a-3p (miR-15a-3p) in controlling ferroptosis in CRC in conjunction with bioinformatics analysis methods [24]. The experimental results revealed that miR-15a-3p targeted GPX4 and inhibited its expression *in vitro* and *in vivo*, resulting in enhanced erastin-induced ferroptosis and antitumor effects. This result suggests that exploring new targets to control the expression of ferroptosis-sensitive factors through genetic techniques may provide new strategies for precisely treating CRC.

The p53 gene is a tumor suppressor that plays an essential regulatory role in maintaining cellular redox homeostasis. Recent studies have identified p53 as a DNA-binding transcription factor that bidirectionally regulates cellular susceptibility to ferroptosis, which may depend on the p53 variant and the tumor context [25]. On the one hand, it is widely believed that p53 inhibits cystine uptake through transcriptional targeting of SLC7A11 and indirectly activates the function of arachidonic acid 12-lipoxygenase (ALOX12) to sensitize tumor cells to ferroptosis [26]. Meanwhile, it has also been found that wild-type p53 activates CDKN1A/p21 in a transcription-dependent manner to enhance GSH retention in response to metabolic stress induced by cystine deprivation [27]. The p53 gene has been suggested to be a pivotal regulator of erastin-induced ferroptosis in CRC cells. The absence

Table 2 – Applications of ferroptosis in CRC.

Compound/target	Model	Functional mechanism	Effect	Refs.
Cisplatin	HCT116 cells	GSH depletion and GPX4 inactivation	Induction	
Sorafenib	HCT116/HT-29 cells	Sorafenib inhibits system Xc^- and prevents cystine import	Induction	[102]
Cetuximab	HCT116/DLD1/LOVO/SW480 cells; xenograft nude mouse model	Cetuximab promotes RSL3-induced ferroptosis by inhibiting the Nrf2/HO-1	Induction	[18]
β-elemene	HCT116/Lovo cells; orthotopic murine colon cancer model	Combinative treatment of cetuximab and β-elemene induced ferroptosis through GSH depletion, ROS accumulation, and lipid peroxidation	Induction	[19]
IMCA	DLD1/HCT116 cells	IMCA induces ferroptosis by downregulating SLC7A11 through the AMPK/mTOR pathway	Induction	[111]
Apatinib	HCT116 cells	Apatinib targeting ELOVL6/ACSL4, increases ROS levels	Induction	[112]
Dihydroartemisinin (DHA)	CT26/MC38 cells	Codelivery of DHA and iron increases ROS level, lipid peroxidation and tumor immunogenicity	Induction	[36]
RSL3	HCT116/LoVo/HT29 cells	RSL3 promotes ferroptosis-related LIP increase and ROS accumulation by inhibiting GPX4	Induction	[113]
TP53	HCT116/SW48 cells; Tumor-bearing mice	TP53 suppresses erastin-induced iron death by inhibiting DPP4 activity in a transcription non-dependent way	Inhibition	
microRNA-15a-3p	HCT-116/CaCo2/HT29/KM12 cells CRC patient samples	MiR-15a-3p enhances erastin-induced ferroptosis by directly targeting GPX4	Induction	[24]
Andrographis	HCT116 and SW480 cells; xenograft animal model;patient-derived tumor organoids	Andrographis promotes the expression of ferroptosis-related genes (HMOX1, GCLM, and GCLC) to reduce the resistance of CRC to 5-FU	Induction	[114]
Propofol	NCM460/SW480 cells; CRC patient samples	Propofol triggers ferroptosis in CRC cells by inhibiting GPX4 expression and downregulating STAT3 expression	Induction	[115]

Table 3 – Ferroptosis-associated genes are used as diagnostic and prognostic markers for CRC.

Ferroptosis related genes	Refs.
ACACA, GSS, and NFS1	[116]
MT1G	[117]
lncRNAs (AP003555.1, AC099850.3, AL031985.3, LINC01857, STPG3-AS1, AL137782.1, AC124067.4, AC012313.5, AC083900.1, AC010973.2, ALMS1-IT1, AC013652.1, AC133540.1, AP006621.2 and AC018653.3)	[118]
NOS2, ALOXE3, and IFNG	[119]
SLC2A3, ATF3, VLDLR, TXNIP, ZFP69B, ABCC1, NFS1, RRM2, and BID	[120]
FDFT1, DUOX1, ALOX12B, ATG13, CAV1, NOS2, JDP2, DRD4, TFAP2C, and PLIN4	[121]

of the p53 gene in CRC cells increases the inhibition of glutamate release and fosters plasma membrane-associated dipeptidyl peptidase 4 (DPP4)-dependent lipid peroxidation to enhance the anticancer activity of erastin *in vivo* [28].

Deletion or mutation of p53 is strongly associated with cancer susceptibility, and p53 mutations are found in more than 50% of CRC cases [29]. Consequently, exploiting the unique metabolic role of p53 to enhance the sensitivity of tumor cells to ferroptosis may be helpful for the precise treatment of CRC patients. Meanwhile, in a recent study, Lv et al. identified the ubiquitin E3 ligase Cullin-9 (CUL9) as an essential regulator of ferroptosis in CRC, with a significant correlation between its expression and the p53 signaling pathway [30]. The authors further evaluated the ferroptotic role of CUL9 in different CRC cell lines. In the TP53wt cell lines, overexpression of CUL9 significantly affected resistance to erastin-induced ferroptosis, whereas the same phenomenon was not observed in the TP53mt CRC cell line Caco2 [30]. Therefore, targeting p53 and p53-mediated ferroptosis is desirable in CRC therapy, but the multiple regulatory factors in the p53-ferroptosis pathway should be carefully considered.

The development of CRC also depends on the close interaction of the mutated cells with their TME, which influences all processes from normal intestinal epithelium to adenomatous polyps and ultimately infiltrates colon cancer [31]. The TME comprises multiple components, including tumor cells, stromal cells (e.g., cancer-associated fibroblasts, CAFs), vascular cells, infiltrating immune cells, extracellular matrix, and multiple secreted factors [32]. Recent studies suggest that ferroptosis can affect tumor immunity by modulating adaptive immune responses. Various types of immune cells in the TME exhibit different responses to ferroptosis. For example, activated $CD8^+T$ cells trigger the

downregulation of SLC7A11 expression in tumor cells by releasing IFN-γ, impairing cystine uptake, and contributing to lipid peroxidation [11].

Moreover, tumor cells undergoing ferroptosis can release damage-associated molecular pattern (DAMP) signals such as ATP, high-mobility group box protein 1 (HMGB1), and calreticulin on the cell surface (ecto-CRT) from cancer cells [33], which enable dendritic cells (DCs) and tumor-associated macrophages (TAMs) to target dying tumor cells precisely and trigger a vaccination-like effect [34]. Dihydroartemisinin (DHA) induces ferroptosis by activating LOX to promote cell membrane lipid peroxidation [35]. Lin et al. found that DHA effectively induced the translocation of calreticulin to tumor cells and increased the emission of the proinflammatory cytokine HMGB-1, which augmented the immunogenicity of CT26 cells by triggering ER stress ROS production [36]. The combined effect of exogenous iron complexes and DHA enhanced the number of specific $CD8^+T$ cells and IFN-γ in the CT26 mouse model, causing significant tumor suppression *in vivo*.

Recent studies have also identified a role for GPX4 in tumor immunity. Regulatory T cells (Tregs) enable the body to maintain immune homeostasis. Nevertheless, Tregs can promote tumor cells in the TME to evade the body's immune surveillance. GPX4-deficient Tregs exhibit abnormal accumulation of lipid peroxides with increased mitochondrial superoxide production, which enhances the antitumor immune response by triggering ferroptosis [37]. In summary, the utilization of ferroptosis to influence the regulation of immune cells in the TME may guide a new direction for tumor immunotherapy in CRC.

Liver metastases represent most of the causes of death in patients with CRC. Therefore, new valuable therapeutic approaches are urgently needed. However, the detailed mechanisms underlying the metastasis of CRC cells to the liver have not been fully clarified. Some evidence suggests that tumor metastasis may depend on EMT and the TME interactions [38,39]. With the continuous research on the complex biology of CRC, scientists found that EMT may play a critical role in the initiation of tumor spread by achieving mobility and aggressiveness [40], and targeting EMT in CRC may be a new therapeutic strategy to prevent liver metastases. While sensitive cancer cells and organoids with a treatment-resistant high mesenchymal state were selectively sensitive to inhibition of GPX4 [9]. By analyzing the composition and characteristics of the tumor immune microenvironment (TIME) in CRC liver metastases with single-cell transcriptome analysis [38], researchers identify ferroptosis as a significant enrichment pathway for tumor-associated neutrophils. Therefore, targeting ferroptosis may overcome conventional CRC drug resistance and impede liver metastases, which have a clinical translation potential [41,42].

Recent studies have shown that erastin attenuates the stemness and chemoresistance of CRC cells [43]. Notably, the redox levels in colon cancer cells also differed from those in normal colon cells, with decreased ROS, GSH levels and pH evident in colon cancer cells compared to normal colon cells [44]. Targeting cellular energy metabolism-mediated ferroptosis for CRC treatment is a promising research direction. On the other hand, iron homeostasis is tightly regulated at the cellular and systemic levels, and the intestine is a crucial site for controlling the balance of iron absorption and output [45]. Consequently, CRC may be more sensitive to regulating iron metabolism than other tumor types. For example, the expression of genes (Divalent Metal Transporter 1, DMT1 and TFR1) related to iron uptake is upregulated in CRC, while the expression of the iron export protein (FPN) is decreased in advanced CRC [46]. In addition, primary and metastatic CRC tumors often exhibit higher glucose consumption than the surrounding normal intestinal tissue, resulting in an acidic TME, which is an essential factor in stimulating resistance to ferroptosis and interfering with its immunogenicity [47]. Therefore, research on ferroptosis may provide new insights into the pathogenesis and clinical treatment of CRC. It should be noted that excess iron can promote tumor growth. Some studies have conclusively demonstrated that iron overload may enhance the resistance of colon cancer cells to lipid peroxidation by activating Nrf2 expression and upregulating the Warburg effect, which promotes the proliferation of CRC cells [48,49]. Therefore, given the complex regulatory role of ferroptosis, precisely and accurately quantifying the ferroptosis response, especially within the complex gastrointestinal environment, remains a significant challenge.

3. Current status of research on ferroptosis-based nano-DDSs for CRC

With the emerging concept of "precision medicine," state-of-the-art nano-DDSs have become a vivid field for efficient tumor-targeted drug delivery. The nanoparticles can also be modified to accomplish their active response to tumor cell surface markers or the surrounding environment and trigger internalization, ultimately achieving optimization of pharmacokinetics and pharmacodynamics. Evidence suggests that abnormal iron metabolism is associated with multiple oncogenic pathways *in vivo*. Using ferroptosis inducers can also assist in overcoming drug resistance and preventing tumor metastasis [50]. Therefore, the combination of ferroptosis with nano-DDSs has emerged as a new biomedical breakthrough in cancer treatment and research hotspots. This section describes several promising ferroptosis-based nanodelivery options for CRC therapy.

3.1. *Nano-DDSs directly drive ferroptosis in tumor cells*

The exquisite balance of ROS and antioxidant networks is vital for maintaining redox homeostasis in cells. The metabolically active tumor cells can generate more H_2O_2 than normal tissues, providing a suitable reaction environment for using iron ions to catalyze the Fenton reaction. Notably, the induction of ferroptosis directly with Fe^{2+} is usually ineffective due to the protection of the cell membrane and the defense mechanism of the TME. Consequently, designing novel nano-DDSs to increase the iron release efficiency contributes to the benefit of CRC-targeted therapy, which can bypass the selective permeability of the cell membrane. Iron-based nanoparticles can be decomposed and metabolized

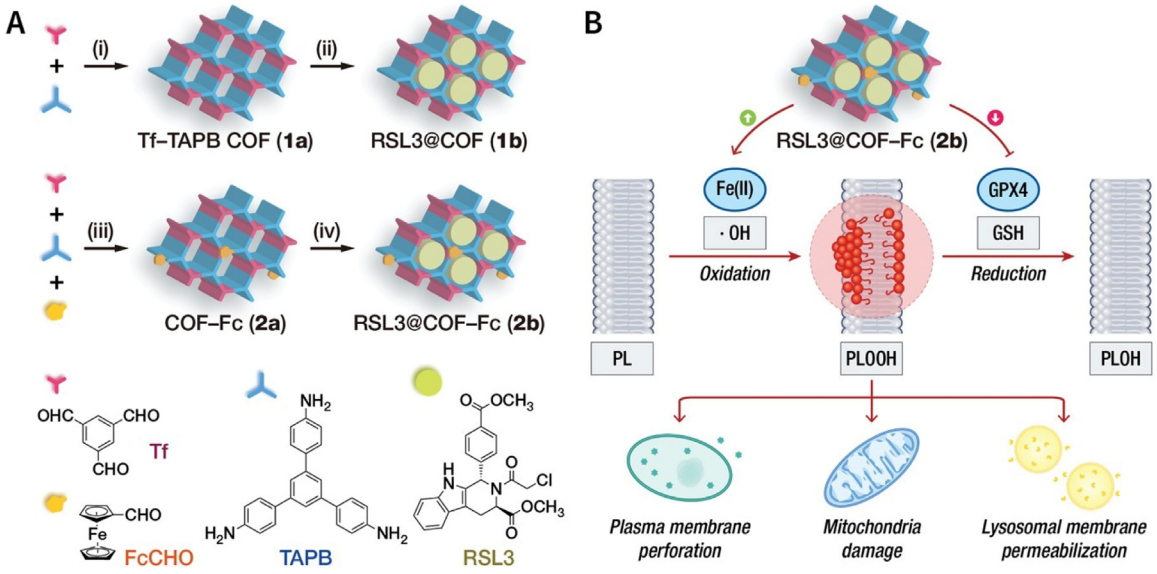

Fig. 2 – Demonstration of (A) preparation of RSL3@COF-Fc (2b) and (B) ferroptosis therapeutic pathway of RSL3@COF-Fc (2b). Reprinted with permission from [55] Copyright 2021, WILEY.

by the acidic lysosomes of tumor cells, releasing Fe^{2+} and Fe^{3+} [51]. Xu et al. assembled ferric ions with vitamin K3 derivative 6-[2-(3-*methyl*)-*naphthoquinolyl*]-hexanoic acid (NQA) in coordination to obtain Fe-NQA nanopolymer particles (Fe-NQA NPs) with multifunctionalities, which exhibited excellent tumor inhibition (73.67%, 25 mg/kg) in a mouse CT26 model [52]. After entering the cells, NQA produces substantial levels of ROS through the oxidation–reduction cycle of semiquinone free radicals while reducing the accompanying Fe^{3+} to Fe^{2+} to spark the Fenton reaction. In addition, the nano-DDS significantly depressed the activity of GSH, thioredoxin, and other antioxidant substances in CT26 cells, which decreased the protective effect of antioxidant function on cells and inhibited the metastasis of tumors. An ultrasmall single-crystal Fe nanoparticle (bcc-USINPs) composed of an oxide shell (Fe_3O_4) and a zero-valent Fe(0) core was designed by Liang et al. [53]. It could be observed that the Fe_3O_4 shell prevents the oxidation of the Fe(0) core in a physiological environment. When such nanoparticles reach the acidic TME, the exposed Fe(0) core shows excellent Fenton catalytic activity, displaying significant tumor suppression and ferroptosis in various tumor cell lines (HepG2, MC38, and 4T1). The researchers found that bcc-USINPs induce immunogenic cell death (ICD) in tumor cells and further trigger DC maturation-enhanced tumor T-cell infiltration. After modification by the iRGD peptide, iRGD-bcc-USINP-induced ferroptosis is highly immunogenic and stimulates antigen presentation. Combining this therapy with PD-L1 immune checkpoint blockade treatment successfully generated strong immune memory and inhibited tumor growth in MC38 tumor-bearing C57BL/6 mice.

In addition to using iron-based nano-DDSs to provide exogenous iron ions to accelerate the Fenton reaction, rationally designed organic nano-DDSs can also manipulate ROS levels to drive ferroptosis. Lee et al. constructed a pH-sensitive PolyCAFe micelle, loading benzoyloxycinnamaldehyde (BCA) and ferrocene in its hydrophobic framework. It takes advantage of releasing H_2O_2 and Fe^{2+} by BCA and ferrocene in weakly acidic environments to stimulate the Fenton reaction, generating an excess of ROS [54]. *In vitro* and *in vivo* experiments showed that this nano-DDS was readily taken up by cells via endocytosis, released BCA, and caused a considerable increase in ROS stress in a concentration-dependent manner. It was well targeted in SW620 cell-loaded mice, significantly reducing tumor volume and causing no significant body weight changes. This single-component nano-DDS has superior clinical conversion potential due to H_2O_2 generators and iron loading in the same polymer backbone.

Similarly, a nano-DDS RSL3@COF-Fc (2b) (Fig. 2) loaded with ferrocene (Fc) and RSL3 was developed to drive redox imbalance in tumor cells [55]. After the covalent organic framework (COF) was endocytosed into tumor cells, FcCHO acted as a Fenton-like reaction catalyst, and the slow release of RSL3 remarkably inhibited GPX4. *In vitro* experiments showed that lipid peroxidation was significantly increased in HCT116 cells after this nano-DDS treatment. This result suggests that we could design nano-DDSs with more functions and activities by reprogramming these emerging nanomaterials at the molecular and atomic structure levels.

Ferritin (Fn) is an iron storage protein with a hollow cavity structure that can release iron in a controlled manner. It consists of 24 polypeptide chains with an outer diameter of approximately 12 nm and an inner lumen diameter of approximately 8 nm [56]. As a human endogenous protein, its unique cage-like structure endows it with low immunogenicity, high stability, modifiability, and superior biocompatibility [57]. Emerging studies have shown that the NCOA4-mediated autophagy pathway can lead to ferritin degradation, increase intracellular unstable iron content, and rapidly accumulate ROS, disrupting iron homeostasis and

metabolism in tumor cells [58]. There is a broad scope for applying Fn as a nanocarrier for drug delivery. Yang et al. designed a nanoparticle (Fn-DOX) composed of the antitumor drug doxorubicin (DOX) and exogenous Fn [59]. On the one hand, Fn can serve as a vector to target tumor cells such as CRC cells that overexpress transferrin receptor 1 (TFR1) while increasing the intracellular iron concentration to a certain extent [60]. On the other hand, the classical chemotherapeutic drug DOX acts as an electron acceptor in redox reactions to increase the production of mitochondrial ROS [61]. Fn-DOX reduced the cardiotoxicity of DOX by targeted administration and enhanced the targeted lysis of HT29 cells by ferroptosis.

3.2. *Nano-DDSs targeting TME and cancer stem cells (CSCs)*

Most nanotechnology-based studies have concentrated on cancer cells rather than other critical components of the TME. However, due to the higher pressure of the tumor tissue, it is harder for the nanocarriers to penetrate and approach the targeting site. Meanwhile, the mild acidity, rich angiogenesis, and hypoxia of TME conditions (Fig. 3) attenuate the delivery and effectiveness of conventional cytotoxic therapies but contribute to the accumulation of actively targeted nanoparticles [62]. In CRC therapy, it may be more advantageous and promising to target genetically stable nontumor cells in the TME than drug-resistant tumor cells, which are highly susceptible to mutations. CAFs play a key role in cancer cell progression and invasion by expressing multiple tumorigenic factors. CAFs also upregulate FASL and PD-L2 molecules acting on T cells, causing tumor-specific T-cell dysfunction or death. Multiple molecules, such as fibroblast activating protein-α (FAP), fibroblast growth factor receptor (FGFR), and α-SMA, are overexpressed in CAFs, which could offer suitable targets to treat cancer in the TME [63]. Cheng et al. developed an exosome-like nanocapsule (eNV-FAP). This nanovaccine can be easily prepared in significant quantities using a small extruder by the continuous extrusion of FAP genetically engineered tumor cells [64]. The eNV-FAP vaccine was designed to reshape the TIME by promoting the maturation of DCs, enhancing the lysis of tumor cells and FAP^+CAFs by activated $CD8^+T$ cells, and reducing the proportion of immunosuppressive cells, such as M2-like tumor-associated macrophages (M2-TAMs) and bone marrow-derived suppressor cells (MDSCs), in a colon cancer model. The eNV-FAP immunization group showed a significantly lower tumor formation rate and volume than the control group. Meanwhile, a significant reduction in the number of FAP^+CAFs and a remarkable decrease in the mRNA expression levels of FAP and fibronectin were observed in mouse CT26 tumor tissues after eNV-FAP treatment. In addition, a decrease in SLC7A11, SLC3A2, and GPX4 mRNA expression was observed compared to PBS controls, as opposed to an increase in lipoxygenase 15 (LOX15), suggesting that the nano-DDS may stimulate antitumor immunity and initiate ferroptosis in tumors at the same time.

In CRC, the rapid proliferation of tumor cells often leads to defective tumor microvasculature, where inadequate blood supply or hypoxia is a typical feature of the microenvironment in almost all solid tumors [65]. Tumor cells rapidly adapt to hypoxic stress and undergo genetic transformation through hypoxia-induced factors (HIFs) [66]. Hence, designing nano-DDSs with hypoxia-sensitive components to enhance drug penetration depth and cytotoxicity may inspire results. Jiang et al. designed a Cu^{2+} hypoxia-triggered liposomal metal-polyphenol-gene bionanoreactor (HLBBRT) to deliver siRNA targeting vascular endothelial growth factor (VEGF) [67]. Under hypoxic conditions, HIF stimulates VEGF mRNA transcription, which is highly correlated with microvessel density and metastasis in CRC [68]. This nano-DDS showed efficient gene delivery and potent tumor-killing immunity in CRCs and its liver metastasis model. Cu^{2+} from the nano-DDS catalyzed a Fenton-like reaction, leading to efficient conversion of H_2O_2 to ROS while depleting intracellular GSH. In a CT26 cell model of liver metastasis, mice in the HLBBRT group had significantly longer survival times, a 4.6-fold and 5.9-fold increase in the efficacy of T cells compared with controls, and upregulation in the production of tumor necrosis factor (TNF)-α and IFN-γ. Consistent with the results of VEGF gene silencing, tumor angiogenesis and HIF-1α protein expression were notably reduced after HLBBRT nanotherapy. Likewise, Jiang et al. synthesized a low oxygen-responsive

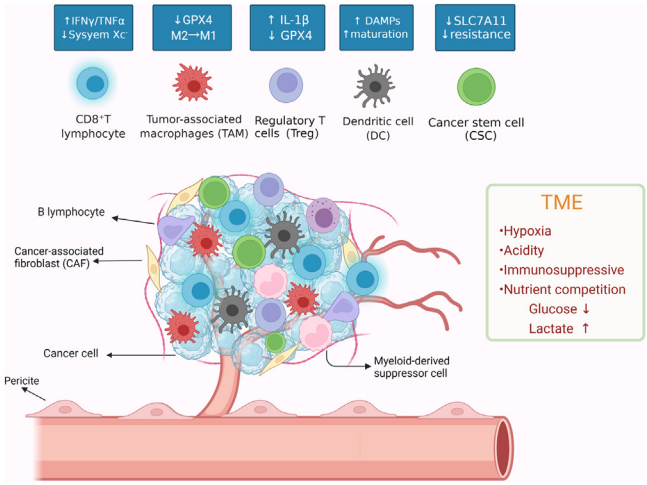

Fig. 3 – Effect of ferroptosis-based nano-DDSs in CRC on the tumor microenvironment and immune cells. The release of IFN-γ and TNF-α from T cells downregulates the expression of SLC3A2 and SLC7A11, thereby reducing the uptake of cystine by tumor cells and increasing the sensitivity of tumor cells to ferroptosis; TAMs are divided into M1 proinflammatory and M2 anti-inflammatory types, which are alternatively activated with different susceptibilities to RSL3-induced ferroptosis. Using ferroptosis-based nano-DDS to drive immune reprogramming to convert the M2 to the M1 phenotype is a promising therapeutic target; GPX4 deletion in Tregs leads to ferroptosis and promotes IL-1β production, thereby enhancing antitumor immunity. Ferroptosis of tumor cells is accompanied by the release of DAMPs that promote dendritic cell maturation, thus provoking a cytotoxic T-cell-mediated anticancer immune response. CSCs are more iron-dependent, so targeting CSCs by disrupting intracellular iron homeostasis may reduce drug resistance.

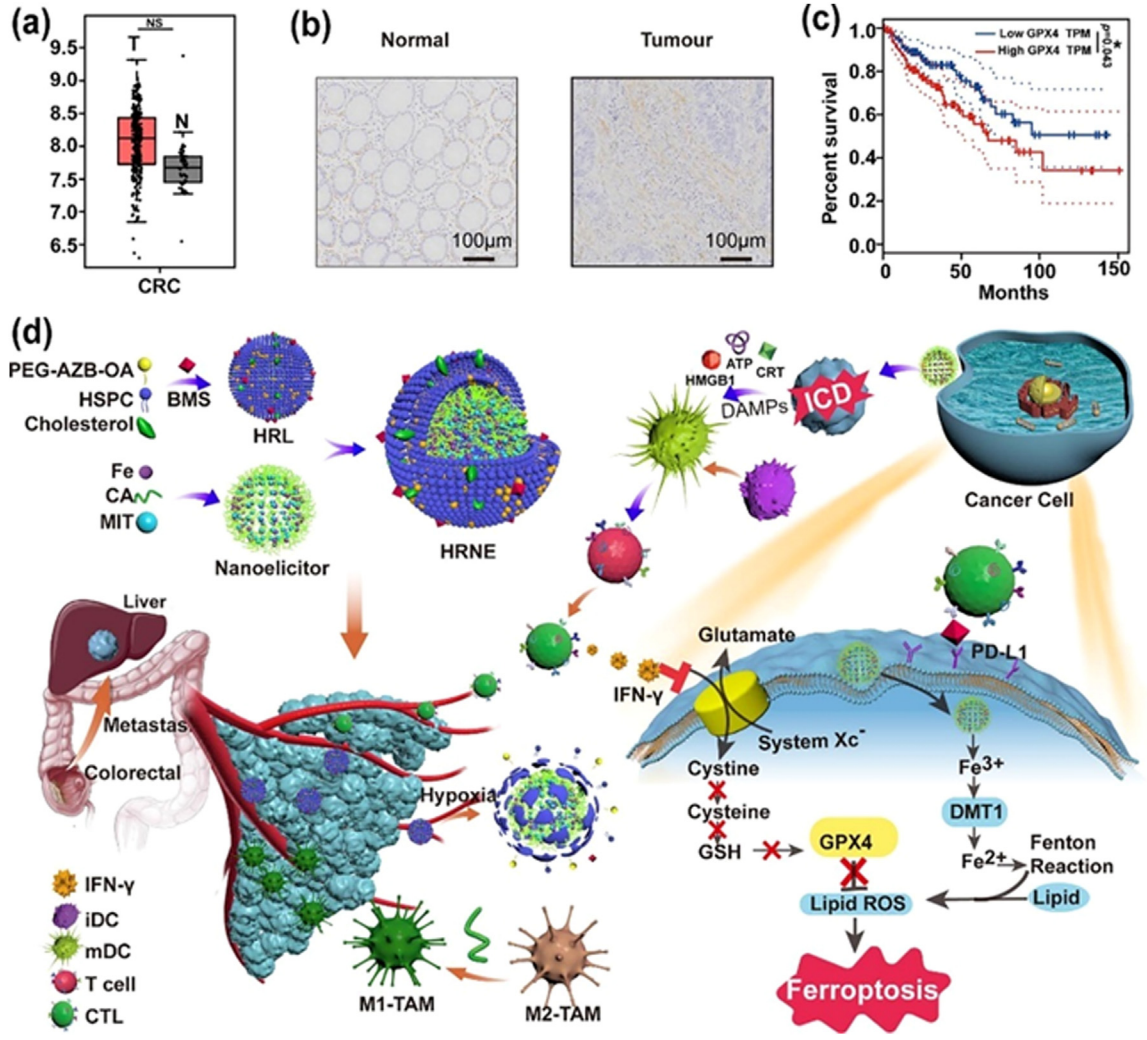

Fig. 4 – Description of the hypoxia-responsive nanoelicitor (HRNE) for ferroptosis-based cancer immunotherapy. (a) Results of bioinformatics analysis of GPX4 gene expression (from CRC patients and normal subjects). (b) Immunohistochemical staining of GPX4 in CRC tissues and normal tissues. (c) Comparison of the overall survival of CRC patients with high or low GPX4 expression. (d) Cell death mechanism and immune response of HRNE by ferroptosis in CRC. Reprinted with permission from Ref. [20] Copyright ©2021 ELSEVIER.

azobenzene (AZB) derivative using oleanolic acid (OA) as the hydrophobic part and polyethylene glycol (PEG) as the hydrophilic group [20] (Fig. 4). PEG-AZB-OA and hydrogenated soy phosphatidylcholine (HSPC) in an aqueous solution can self-assemble into heterogeneous liposomes with low oxygen responsiveness. The hypoxic environment at the tumor site triggers the disintegration of the liposomal shell, releasing the encapsulated Fe^{3+} ions and two immune-inducing polyphenols, chlorogenic acid (CA) and mitoxantrone (MIT). The nano-DDS successfully reduced Fe^{3+} to Fe^{2+} by Fenton reaction in CRC and its liver metastasis model, generating large amounts of ROS. Additionally, it stimulated cytotoxic T lymphocytes to release large amounts of IFN-γ through CA and MIT, promoting tumor immunity while blocking the Xc^--GPX4 pathway to deprive cells of resistance to oxidative stress.

The acidic microenvironment arises from the aberrant tumor vascular system and hypoxia. Tumor cells obtain energy from oxygen-independent glycolysis, with excessive glucose-fermenting uptake to lactate, resulting in increased production and excretion of H^+ ions. Based on the acidic microenvironment of tumors, a series of pH-sensitive nano-DDSs have been developed to promote faster nanoparticle diffusion and more effective tumor penetration. Wei et al. used a one-step method to prepare manganese (Mn)-doped mesoporous silica nanoparticles (MMSNs) and loaded sorafenib (SO), an inhibitor of Xc^-, into MMSNs (MMSNs@SO) (Fig. 5A) with a drug loading rate of 2.68% ± 0.32% [69]. The action mechanism can be understood as the degradation of nanoparticles in an acidic and GSH environment, releasing SO accompanied by GSH depletion (Fig. 5C&5D). The released SO inhibits SLC7A11 and impedes further GSH biosynthesis. The nanoparticles can induce ferroptosis in liver tumor cells by achieving pH-responsive drug release in the TME, suggesting a new guiding direction for treating advanced CRC liver metastases.

Tumors can be considered heterogeneous tissue whose growth and development depend on CSCs. The progression and metastasis of CRC are associated with CSCs [34].

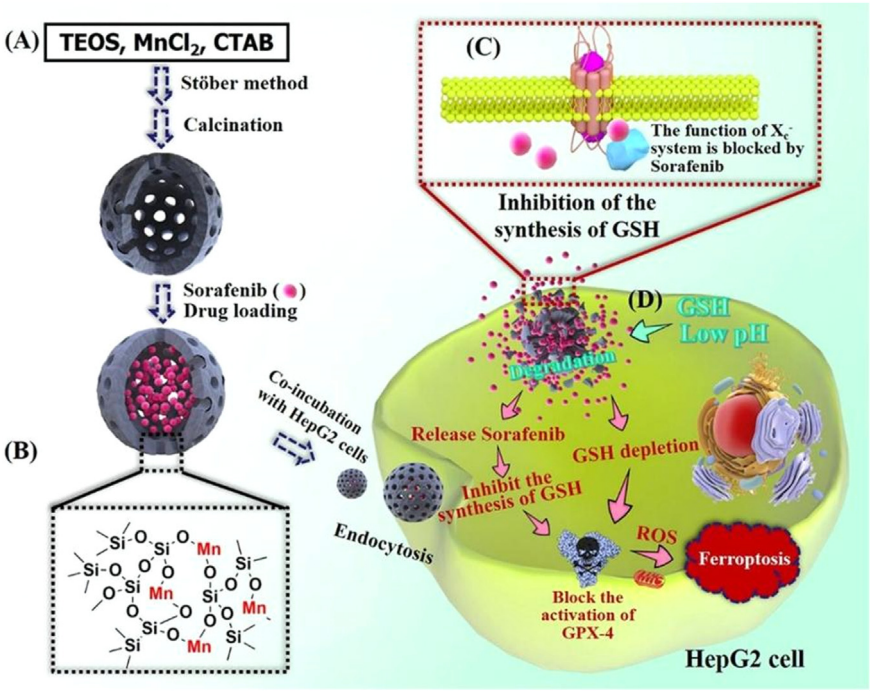

Fig. 5 – Schematic representation of the synergistic action of constructing manganese-silica nanoparticles (MMSNs) with sorafenib (SO) MMSNs@SO. (A and B) Preparation process and structure of MMSNs@SO nanoparticles; (C and D) Mechanism of ferroptosis induced by MMSNs and SO. Reprinted with permission from [69] Copyright ©2019 ELSEVIER.

Furthermore, through activation of self-renewal, epigenetic regulation, and metabolite reprogramming, CSC-related markers (CD44, CD133, etc.) and pluripotent transcription factors (Sox2, NANOG, and OCT4) may be more efficient in extracting iron from the TME [70]. Meanwhile, cisplatin-resistant HT29 cells have greater stemness and ferroptosis sensitivity than parental HT29 cells [43]. The results showed that the CSCs antagonized by SLC7A11 had higher ROS levels and weaker chemoresistance. Therefore, manipulating iron accumulation to induce ferroptosis may be an effective strategy for targeting CSCs [71]. Salinomycin (SAL) interferes with intracellular iron metabolism. It acts as an ion carrier for mitochondrial K^+ channels, suggesting that mitochondrial damage associated with RAS activation synergizes with SAL-induced alterations in intramitochondrial homeostasis [72]. This suggests that SAL has the potential to induce ferroptosis in CSCs, but its high toxicity limits its clinical use. Tsakiris et al. encapsulated the active form of irinotecan SN38 with SAL into lipid nanocapsules and applied it in a mouse CRC model [73]. The combination of microencapsulated SN38 and SAL was effective in targeting CSCs, with a 1.8-fold increase in the median survival of mice in the nanocoadministration group compared to the untreated group and a reduction in side effects.

With the development of microbiome studies and high-throughput sequencing technologies, several data support that intestinal flora, as critical contributors to the TME, can influence the development of CRC through a range of metabolic and structural changes [74]. An imbalanced gut microbiome releases large amounts of bacterial toxins and carcinogenic metabolites that compromise the barrier function of preexisting epithelial cells, leading to dysregulation of the immune and inflammatory systems and thus triggering CRC. Therefore, targeting and eliminating undesirable flora metabolites that may be responsible for CRC can be an effective strategy for designing nano-DDSs. Endogenous H_2S can be considered a tumor growth factor vital in maintaining CRC cell growth, proliferation, and angiogenesis [75]. A nano-DDS (VZnO) with virus-like mesoporous silica nanoparticles (VMSN) as a carrier and a ZnO layer deposited on its surface can effectively reduce the H_2S content in CRC [76] (Fig. 6). This nano-DDS, while depleting H_2S, was accompanied by a significant decrease in the expression levels of GSH and GPX4 detected in HCT116 and CT26 cells, indicating that ferroptosis was activated. The investigators further explored the potential molecular mechanism of ferroptosis activation after treatment by RNA-seq-based transcriptome analysis. They found that VZnO may disrupt the antioxidant-protective state of GSH on cells by significantly downregulating γ-glutamylcyclotransferase (GGCT). This innovative research idea of combining ferroptosis also provides a new perspective for designing nano-DDSs to target the TME of CRC.

3.3. *Emerging combination therapy based on nano-DDSs*

Growing evidence suggests that monotherapy in cancer treatment to induce ferroptosis is usually effective at the cellular level. However, given the complexity and heterogeneity of CRC, monotherapy often struggles to achieve tumor ablation *in vivo*, leading to tumor recurrence and metastasis. Combining multiple therapeutic strategies via

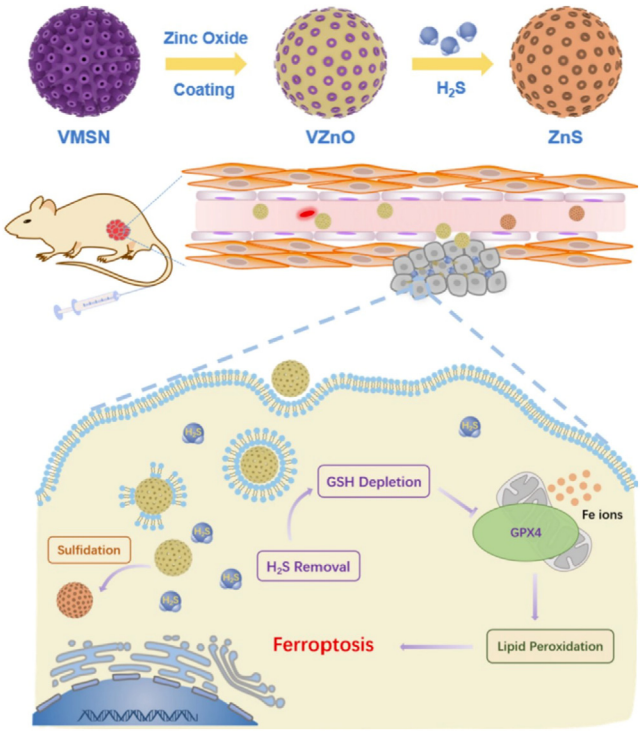

Fig. 6 – Schematic diagram of a zinc oxide-coated virus-like silica nanoparticle (VZnO) acting on CRC to remove H2S while depleting GSH to activate ferroptosis. Reprinted with permission from [76] Copyright ©2021 Springer Nature.

sophisticated nano-DDSs inhibits tumor cell proliferation through distinct targets and mechanisms with reduced toxic side effects. This section describes ferroptosis-based nano-DDSs in conjunction with other therapeutic modalities (e.g., gene therapy, phototherapy, and immunotherapy) in combating CRC.

3.3.1. *Gene therapy*

The three main pathways of CRC carcinogenesis currently include DNA replication, chromosomal instability, and epigenetic regulation [77]. The application of precision medicine based on individual genomic and molecular pathways of tumor growth/proliferation dramatically benefits the targeted therapy and immunotherapy of patients with advanced CRC. Nuclear factor-κB (NF-κB) is an important class of regulatory transcription factors that can function in different stages of cancer immunity through aberrant activation [78]. In CRC, the NF-κB signaling pathway promotes tumor cell proliferation, metastasis, and drug resistance through the upregulation of antiapoptotic genes [79]. Wang et al. developed gene interference ferroptosis therapy (GIFT) for cancer treatment [80]. This approach specifically increased intracellular ROS levels in multiple tumor cells by knocking down the expression of two iron metabolism genes, FPN2 and LCN2, through CRISPR/Cas13a and miRNA, demonstrating significant tumor growth inhibition and survival improvement in CT26 tumor-bearing mice. The researchers first designed a gene expression vector to regulate intracellular NF-κB activity, containing two sequence elements: the promoter and gene coding [81]. The decoy minimal promoter (DMP) consists of an NF-κB decoy sequence and a minimal promoter sequence, which is a double-stranded DNA fragment containing an NF-κB binding site that regulates the expression of NF-κB target genes by interfering with the transference of activated NF-κB into the nucleus [82]. The introduction of 2,3-dimercaptosuccinic acid (DMSA)-coated Fe_3O_4 nanoparticles (FeNPs) is also one of the innovations of this therapeutic approach. The surface modification of Fe nanoparticles with DMSA resulted in reduced toxicity and significantly improved biocompatibility of FeNPs, which led to a compensatory cellular response to the transcriptional regulation of genes that maintain intracellular iron and osmotic homeostases, such as Tfrc, Trf, LCN2, and Slc5a3.

3.3.2. *Phototherapy*

Phototherapy is a treatment to ablate tumors by irradiating the lesion area with light sources, especially near-infrared light sources, which are minimally invasive and controllable modalities [83]. For multimodal ferroptosis-driven cancer therapy, combining phototherapy or imaging techniques and ferroptosis has been studied extensively [84]. Introducing nano-DDSs can help improve delivery efficiency by integrating drugs and photosensitizers into the same platform.

Photothermal therapy (PTT) can precisely target tumors by varying the size and intensity of the laser. When PTT is employed in combination therapy, heat therapy dramatically increases the rate of chemical reactions (e.g., Fenton-like reactions) and intracellular enzyme activity, disrupting the inherent resistance of cells to tumor treatment (e.g., ferroptosis-associated proteins, liable iron pools, and respiratory enzymes) [85]. Cao et al. prepared SRF@MPDA-SPIO nanoparticles corresponding to environmental factors such as pH, temperature, and GSH by loading sorafenib (SRF) with ultrasmall paramagnetic iron oxide (SPIO) into mesopores and surfaces of mesoporous polydopamine (MPDA) by the nano casting technique and were able to exert ferroptosis effects on tumor cells under the guided treatment of magnetic resonance [86] (Fig. 7). The results showed that the nanodrug could effectively inhibit the growth of human colon cancer HCT116 cells, and tumor regression was even observed in the SRF@MPDA-SPIO plus laser treatment group in mice receiving the combined ferroptosis/PTT treatment.

Photodynamic therapy (PDT) employs specific wavelengths to irradiate the lesion site, activating photosensitizing drugs that selectively accumulate in the lesion tissue and producing many site-specific ROS to destroy the tumor [87]. As a source of ROS for the Fenton reaction, PDT can enhance lipid autoxidation and improve the efficacy of PDT in cancer therapy. In this regard, an ingenious strategy has been developed based on a nanoscale iron oxide-loaded porphyrin-grafted lipid nano-DDS (Fe_3O_4@PGL NPs) under the guidance of bimodal MR/fluorescence imaging, which almost completely inhibited the growth of HT29 tumor cells by enhancing PDT [88]. Further experimental results showed that the nano-DDS produced more significant antitumor effects by accelerating the Fenton reaction and inducing oxidative stress in TAMs in the TME. Zhou et al. successfully developed novel H_2S-responsive oxidized-iron hydroxide

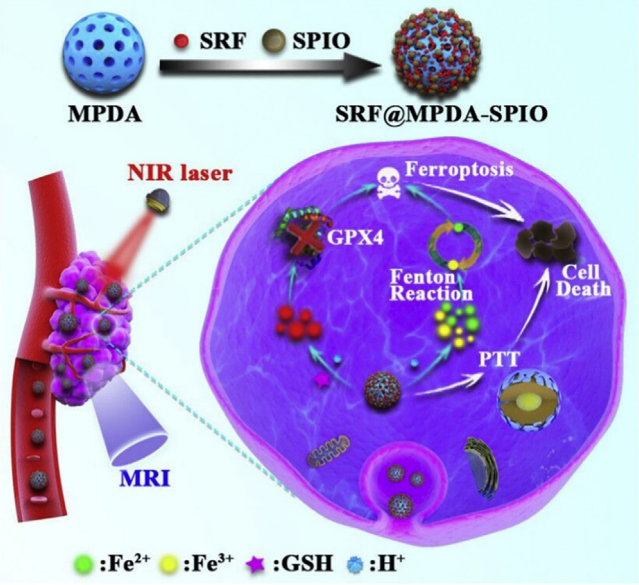

Fig. 7 – Schematic illustration of the multiresponse nano-DDS (SRF@MPDA-SPIO) to pH, temperature and GSH for combined ferroptosis and PTT. Reprinted with permission from [86] Copyright© 2020 ELSEVIER.

nanospinels (FeOOH NSs) for the cotreatment of colon cancer. FeOOH NSs effectively adsorbed endogenous H_2S from CT26 colon tumors, and the FeS generated by the reduction reaction could affect the expression of GPX4 in tumor cells [89]. Simultaneously, the overexpressed H_2S-driven cascade-generated FeS displayed NIR-triggered photothermal therapeutic ability. The FeS and FeOOH-PEG NSs rapidly increased to 50 °C after 100 s of NIR irradiation, effectively promoting the necrosis and apoptosis of cancer cells. In the CT26 tumor-bearing mouse model, administration of FeOOH NSs effectively cleared endogenous H_2S. Eventually, it reduced the relative tumor volume from 67 ± 16.2 to 21.1 ± 8.2, while the combined photothermal treatment further reduced the tumor volume to 14 ± 4.6.

3.3.3. *Immunotherapy*

Desirable cancer therapy should act on the primary tumor and induce systemic antitumor immunity for long-lasting efficacy and suppression of metastatic tumors. Several extensive studies have shown that the lymphocyte response is an essential prognostic factor in CRC. Some patients with advanced CRC (mismatch repair-deficient mutations or high microsatellite instability) could benefit from immunotherapy with programmed cell death protein 1 (PD1) inhibitors [90]. Tumor cells undergoing ferroptosis are highly immunogenic, fully activating the immune response and triggering antigen-specific immunity against the tumor [91]. A nano-DDS (CISAR) based on photothermal enhanced ferroptosis and immunotherapy consisting of copper and iron silicate, with photothermal agent gold nanoparticles and immune agonist R848, successfully induced ROS-enhanced ferroptosis in CT26 tumor cells [92].

On the other hand, tumor-associated antigens released from dead tumor cells enhance antitumor immune responses by promoting DC maturation and T-cell infiltration. IFN-γ released from $CD8^+T$ cells further downregulates the expression of SLC7A11 and GPX4, promoting lipid peroxidation in tumor cells to retrigger ferroptosis. This study sheds new light on immunotherapy in eliminating primary and metastatic CRC.

3.4. *Nano-DDSs against multidrug resistance (MDR)*

Resistance to multiple therapeutic strategies remains the main culprit for treatment failure in CRC patients. MDR in tumors is a complex process involving multiple genes and signaling pathways, which can be divided into intrinsic and acquired resistance [93]. Alterations in various genes and pathway patterns provide a survival advantage for drug-resistant cells over drug-sensitive cells, leading to the formation of drug-resistant tumors. Combination therapy is one of the most essential tools to overcome MDR, and there is growing evidence that drug-resistant cancer cells are sensitive to ferroptosis. Given the active iron metabolism in cancer cells, advanced nano-DDSs to trigger cellular ferroptosis and reverse drug resistance are an excellent option. The high expression of P-glycoprotein (P-GP) in CRC cells is one of the main reasons for the failure of chemotherapeutic drug efflux. A thin-film hydration method was used by Huang et al. to coencapsulate DHA and DOX into mannose-based liposomes [94]. DHA resensitizes HCT8/ADR tumor cells to DOX, and the two drugs have synergistic effects on drug-resistant colon cancer, manifested by downregulation of the antiapoptotic protein Bcl-xl and induction of autophagy. The introduction of mannosylated liposomes significantly improved the intracellular delivery of DOX and DHA, improving nuclear distribution and *in vivo* therapeutic efficacy.

4. Conclusion and perspective

In this review, we provide a systematic insight into the progress in ferroptosis- based CRC therapy, with particular emphasis on applying nano-DDSs as strategies for the induction of ferroptosis (Table 4). Several advances have been made in exploring ferroptosis in CRC at the molecular level. In preclinical animal models, the underlying mechanisms by which ferroptosis occurs are complex, involving both enzymatic systems and metabolic networks of multiple targets associated with the pathophysiological conditions of the tissue. Therefore, to develop a disease-context- dependent therapeutic regimen, there remains a need to analyze the regulatory mechanisms of ferroptosis occurring in CRC in multiple aspects, including metabolic pathways, gene mutations, and epigenetic modifications. We are concerned that ferroptosis appears to be a double-edged sword in the treatment of gastrointestinal disorders. In a mouse model of intestinal ischemia, researchers found that ferroptosis occurs in the early stages of reperfusion, and the inhibition of ferroptosis ameliorates intestinal ischemia/reperfusion-induced intestinal injury [95]. Additionally, recent studies have revealed that dysregulated ferroptosis is associated with the pathogenesis of inflammatory bowel disease [3].

Table 4 – Summary of recently reported ferroptosis-related nano-DDSs for CRC therapy.

Material type	Nanoparticle	Size (nm)	Functional mechanism	Encapsulation	Refs.
Metallic oxide	SRF@MPDA-SPIO	276.6	Fenton reaction, SLC7A11 inhibition, PTT	Sorafenib	[86]
Metallic oxide	Fe_3O_4@PGL NPs	10	Fenton reaction, PDT	Fe_3O_4, porphyrins	[88]
Metallic oxide	FeOOH	80	Fenton reaction, PTT	Fe	[89]
Iron-based nanoparticles	iRGD-bcc-USINPs	3.8 ± 0.8	Fenton reaction, immunotherapy	Fe_3O_4, iRGD	[53]
Iron-based nanoparticles	FeS_2-FA	151	Fenton reaction, GSH depletion, apoptosis	Folate	[122]
Coordination polymer	Fe-NQA NPs	140	Fenton reaction, GPX4 inhibition	Fe, vitamin K_3 derivative	[52]
Coordination polymer	SRF@Fe^{III} TA-MB	220	Fenton reaction, GPX4 inhibition, PDT	Fe^{3+}, tannic acid, sorafenib, methylene blue	[97]
Coordination polymer	macDNA-Fe/PMCS SAzymes	156–226	Fenton reaction, GSH depletion	DNA	[96]
Coordination polymer	$^{PGF}CaCO_3$-PEG	214.8	Fenton reaction, chemotherapy	Cisplatin, gallic acid, Fe^{2+}	[123]
Coordination polymer	FesiRNAPNPs	250	Fenton reaction, GSH depletion, energy metabolism interference	Fe^{2+}, siRNA	[124]
Coordination polymer	ZnP@DHA/Pyro-Fe	90	ROS overloading, increase in tumor immunogenicity	DHA, pyropheophorbide-iron	[36]
Mesoporous silica	VZnO	203	GSH depletion, clearance of H_2S	ZnO	[76]
Mesoporous silica	DMSN/Fe_3O_4–Mn@CB-839	160	GSH depletion, Fenton /Fenton-like reaction	Fe_3O_4, Mn^{2+}, CB-839	[125]
Carbon nanosheets	BN-GDY	2.93 (thickness)	GSH depletion, deactivation of GPX4	Boron and nitrogen atoms	[126]
Exosome-like nanovesicles	eNVs-FAP	168.6 ± 46.08	Downregulating GPX4 by the release of IFN-γ and the depletion of FAP^+CAFs	FAP gene–engineered tumor cells	[64]
Metal-polyphenol nanonetwork, polysaccharide	TA-β-CD@DHA	200	Fenton reaction, GPX4 inhibition	DHA, Fe^{3+}	[127]
Polymer, leukocyte membrane vesicles	GCMNPs	133 ± 5	Fenton reaction, GPX4 inhibition, immunotherapy	Glycyrrhetinic acid, ferumoxytol	[128]
Polymer	MNP@PMPC-SRF	160	Fenton reaction, GPX4 inhibition	Sorafenib, Fe_3O_4	[129]
Protein	Fn-DOX	12.7 ± 4.1	Fenton reaction, chemotherapy	DOX	[59]
Magnesium-aluminum silicate nanosheets	NSs@DCPy	300, 1.1(thickness)	Iron overload, GSH depletion, PDT	DCPy (photosensitizer)	[130]
Self-assembled nanoparticles	Hypoxia-responsive nanoelicitor (HRNE)	112.73	Fenton reaction, GPX4 inhibition, immunotherapy	immune-elicitable polyphenols, Chlorogenic acid, Mitoxantrone, Fe^{3+}	[20]
Covalent organic framework	RSL3@COF-Fc	170	Fenton reaction, GPX4 inhibition	RSL3, ferrocene	[55]

Therefore, it is critical to improve the specificity and control the dose of ferroptosis inducers in CRC treatment to reduce the adverse effects on healthy intestinal tissues.

Ferroptosis-driven nano-DDSs have successfully demonstrated unique advantages in oncology therapy as an emerging and highly prospective drug delivery modality. Several strategies are now widely used to improve the delivery performance of nano-DDSs for treating CRC, including (1) using iron/non-iron-based nanomaterials to introduce exogenous iron targeting to tumor sites. As reservoirs of Fe^{2+} and Fe^{3+}, such nano-DDSs can effectively trigger and enhance ROS levels and lipid peroxidation by strengthening the Fenton reaction [97,123]. In addition, magnetic iron-based nanomaterials can effectively aggregate toward tumors under the modulation of an applied magnetic field, such as iron oxide nanoparticles [88,89]; (2) applying innovative

strategies to increase the loading of ferroptosis inducers on nanocarriers and seeking to target tumor cells and CSCs specially [55,86]; (3) designing nanocarriers that can respond to internal and external stimuli generate large amounts of ROS and consume GSH in tumor cells on demand [20,96]; (4) developing nano-DDSs with multi-functionalities induce ferroptosis, synergize tumor ablative effects, and add imaging or diagnostic capabilities [97,98] to inhibit tumor cell proliferation through different targets and mechanisms. Through the innovative optimization of nanoparticle structures (modulation of particle size, an increase of particle-specific surface area, multifunctional surface modification, etc.), existing nano-DDSs for CRC treatment can overcome the limitations of conventional drug delivery systems, such as non-specific distribution, adverse side effects, and drug resistance. While improving bioavailability and therapeutic efficacy, they also possess good biodegradability and biocompatibility. With in-depth research, the immunosuppressive microenvironment has also been demonstrated as a critical barrier to antitumor immunity in CRC development [99]. Compared to traditional soluble antigens, nano-DDSs can deliver immune cargo (antigens, proteins, immunomodulators, etc.) to the desired site to stimulate a more robust immune response, which modulates the tumor immune microenvironment in CRC. Notably, CRC is a disease with complex pathophysiological changes and a high degree of heterogeneity, showing different genetic and biological alterations in different patients. Although existing nano-DDSs generally show high efficiency in two-dimensional cell culture models and xenograft models, nano-DDSs will encounter complex obstacles (nano-biological interactions in blood, insufficient tissue penetration, loss of targeting ability, etc.) between entering circulation in human patients and their eventual release into the TME at the appropriate dose, which has primarily limited the clinical translation of nanomedicines. In addition, biosafety is a crucial issue to be considered when designing ferroptosis-driven nano-DDSs. For instance, SPIO nanoparticles induce mitochondrial iron overload to catalyze lipid peroxidation and exacerbate ferroptosis in ischemic cardiomyocytes, exacerbating left ventricular remodeling and cardiac deterioration [100]. Due to the complexity of cell structure, the mechanism of iron-based nanomaterials entering tumor cells and their distribution and degradation in the cells are not yet clear. Therefore, tumor characteristics and parameters associated with nano-DDSs should be thoroughly evaluated to achieve precise treatment of CRC before utilizing nanomedicine platforms. In the first step, a precise assessment of cancer staging and TME heterogeneity is needed. In the second step, it is necessary to explore more in-depth information about the relationship between nanoparticle structure and bioactivity, and more attention should be paid to the clinical manifestation of nanomaterial-induced ferroptosis. This way, a valid efficacy and safety evaluation system would be established.

As research proceeds, it is believed that integrating nanomaterials exhibiting good biocompatibility and biodegradability through computational techniques, bioinformatics tools, and appropriate models can lead to several effective nano-DDSs for future CRC treatment. Ferroptosis-driven nano-DDSs are still in their research infancy; their excellent performance and broad clinical translation potential make them significant and worthy of further exploration.

Conflicts of interest

The authors declare no conflict of interest.

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