Review Article

The application of graphene oxide and ferroptosis in the diagnosis and treatment of colorectal cancer: a narrative review

Xiecheng Zhou[1#], Qixing Zhang[2#], Haoran Zhu[1], Jiaying Zhao[1], Yuankun Cai[1^]

[1]Department of General Surgery, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China; [2]Department of Pediatrics, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China

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[#]These authors contributed equally to this work.

Correspondence to: Yuankun Cai, MD. Chief Surgeon of General Surgery, Associate Professor, Department of General Surgery, The Fifth People's Hospital of Shanghai, Fudan University, 801 Heqing Road, Shanghai 200240, China. Email: yuankun@medmail.com.cn.

Background and Objective: Colorectal cancer (CRC), a leading global malignancy, continues to challenge the medical community. Despite advancements in surgical, chemotherapeutic, radiation, targeted, and immunotherapeutic strategies, issues like resistance and side effects persist. This review illuminates the potential of ferroptosis, an emerging non-apoptotic cell death form, and graphene oxide (GO), with its distinctive physicochemical properties, in CRC therapy.

Methods: The databases search included PubMed, Medline and Web of Science. Search terms focused on CRC, graphene, GO, ferroptosis, and related aspects in therapy and drug delivery. The time frame for literature retrieval was up to April 2024. Studies in languages other than English were excluded.

Key Content and Findings: Ferroptosis has been recognized for its role in addressing treatment resistance, a notable hurdle in effective CRC management. This form of cell death offers a promising avenue for enhancing the effectiveness of existing treatments. However, understanding its mechanisms and clinical implications in CRC remains an area of active research, with significant progress required for its practical application. Simultaneously, GO, a versatile two-dimensional material, has demonstrated substantial potential in biomedical applications, especially in cancer therapy. Its high specific surface area and unique π-electron domains facilitate the effective binding of chemotherapy drugs, target genes, and photosensitizers. This makes GO a promising candidate in cancer diagnosis and treatment, particularly through tumor photothermal and photodynamic therapy (PDT). Despite these advancements, GO's clinical application faces challenges, including *in vitro* cytotoxicity and decreased biodegradability, necessitating further research.

Conclusions: This review focuses on the characteristics of GO and ferroptosis, as well as their applications in tumor diagnosis and treatment, with a particular emphasis on their potential in CRC.

Keywords: Colorectal cancer (CRC); graphene; graphene oxide (GO); ferroptosis

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^ ORCID: 0000-0001-9735-200X.

Introduction

Colorectal cancer (CRC), as a global health issue, has been experiencing a continual rise in both incidence and mortality rates worldwide. According to the Global Cancer Statistics Report of 2020, CRC ranks third in incidence and second in mortality among all cancers globally (1,2). It poses a serious challenge to public health, especially in developed countries (3,4). Furthermore, the incidence of CRC is closely associated with lifestyle, dietary habits, and genetic background (5). Despite advancements in treatments such as surgery, chemotherapy, radiation, targeted, and immunotherapy, issues like drug resistance and side effects persist (6-8). This is particularly evident in the treatment of advanced or metastatic CRC (mCRC), where the limitations of current therapies become more pronounced (9,10). Therefore, developing new treatment strategies, especially for drug-resistant tumors, has become a focal point of research. With a deeper understanding of the CRC microenvironment, the role of ferroptosis in its pathologic mechanism has become clearer, offering possibilities for novel treatment strategies (11). Ferroptosis, a new form of programmed cell death, shows great potential in the treatment of CRC. Graphene oxide (GO) and its base materials, known for their unique physicochemical properties, have shown significant potential in biomedicine, particularly in the development of drug delivery systems. Recent studies revealing the diversity of ferroptosis in CRC and its connection with immune responses have provided new directions for utilizing GO and its base materials in the treatment of CRC.

This review aims to assess the application prospects of GO and its base materials in the treatment of CRC, particularly their relationship with ferroptosis in such treatments. We will explore the physicochemical properties of GO, the mechanisms of its integration with ferroptosis, and the challenges and opportunities of these materials in clinical applications. Additionally, we will consider the challenges of novel nanomaterials like GO and the ferroptosis mechanism in cancer diagnosis and treatment. To ensure transparency and adherence to best practices, we present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-1016/rc).

Methods

This review is based on a literature search initially conducted between October 23, 2023, and December 24, 2023, and subsequently updated between March 29, 2024, and April 7, 2024. The databases used for this search included PubMed, Medline and Web of Science (*Table 1*).

GO

Features of the GO structure

Graphene, a nanomaterial with revolutionary characteristics, has garnered immense attention in the scientific community due to its unique physicochemical properties and broad application potential (12). Composed of a single layer of carbon atoms arranged in a two-dimensional hexagonal sp^2 hybridized structure, graphene is notable for its extraordinary physical and chemical properties. These properties include high hardness, high electrical resistance, excellent thermal and electrical conductivity, high transparency, and an almost infinite surface area (13-15). Since its isolation in 2004 by Novoselov *et al.*, graphene has demonstrated immense potential in various application fields due to its large theoretical surface area (2,630 m^2/g) and exceptional mechanical and electronic characteristics. Its applications range from sensors and clean energy devices to the manufacturing of nanocomposites (16,17).

GO is an oxidized variant of graphene, typically produced under stringent oxidizing conditions. GO is characterized by the presence of various oxygen-containing functional groups such as hydroxyl, carboxyl, and epoxy groups. These groups render GO more hydrophilic than graphene. The surfaces and edges of GO are enriched with these oxygen functional groups, providing numerous chemical reaction sites. This abundance of reaction sites not only stabilizes GO in water and organic solvents but also offers multiple opportunities for the synthesis of GO-based functionalized composite materials (17).

Synthesis of GO

The synthesis methods for GO have undergone several evolutions and improvements. Early methods include the one proposed by Benjamin Brodie in 1859, where graphite was treated with potassium chlorate and fuming nitric acid at 60 ℃ for four days. The resulting Brodie's GO (BR-GO) is soluble in water but prone to flocculation in acidic environments. The Staudenmaier method improved upon Brodie's approach by adjusting the addition of chlorate and incorporating sulfuric acid, reducing reaction time and enhancing safety. The properties of the material produced are similar to BR-GO. In 1937, the Hofmann method

Table 1 The search strategy summary

Items	Specification
Date of search	Between October 23, 2023, and December 24, 2023; between March 29, 2024, and April 7, 2024
Databases and other sources searched	PubMed, Medline and Web of Science
Search terms used	Colorectal Cancer, CRC, Colon Cancer, Rectal Cancer, Graphene, Graphene Oxide, GO, Ferroptosis, Mechanism, Therapy, Drug Delivery
Timeframe	Articles published between October 22, 2004, and March 23, 2024
Exclusion criteria	Non-English studies
Selection process	X.Z. conducted the selection; Y.C. approved the selection of studies

utilized potassium chlorate and non-fuming nitric acid to produce Hofmann's GO (HO-GO) with a lower oxygen content, demonstrating the significant impact of nitric acid concentration on the level of oxidation (15,17).

The Hummers method is a safer alternative that avoids the production of explosive chlorine dioxide, utilizing an excess of potassium permanganate, sulfuric acid, and a small amount of sodium nitrate, with a reaction time of about 8 to 12 hours. Improved versions of this method include variations without nitrates, a two-step process, the use of co-oxidants, and low-temperature and room-temperature methods, all aimed at increasing environmental friendliness and yield. This is also one of the most commonly used and effective methods currently for synthesizing GO (13,17,18).

In 2010, the Tour method, a variation of the permanganate method, was introduced. It uses a mixture of phosphoric and sulfuric acids, potassium permanganate, and graphite mixed in an ice bath before heating and stirring, producing GO with a higher yield, higher level of oxidation, and more regular structure (19). Besides, there are other modern methods, including those using potassium chromate combined with perchloric or nitric acid, employing less toxic potassium ferrate as an oxidizer, and electrochemical synthesis pathways. These methods continue to drive the development of GO synthesis technology (20-22).

Applications of GO in tumor diagnosis and treatment

GO has shown significant potential in the field of cancer diagnosis and treatment, with applications spanning early detection, precision drug delivery, therapy enhancement, and treatment monitoring (23-25). As part of biosensors, GO is used to detect cancer biomarkers, enabling early diagnosis and disease monitoring (26). In terms of therapy, GO-based nanomaterials serve as drug carriers, enhancing therapeutic effects and reducing side effects through targeted delivery and controlled release mechanisms (27). Additionally, the unique properties of GO can be utilized to enhance imaging techniques, improving the accuracy of cancer diagnosis (23). Overall, as a multifunctional material, GO plays a pivotal role in the diagnosis and treatment of cancer. Its unique chemical and physical properties make it highly applicable in modern medicine.

Photothermal therapy (PTT)

GO exhibits notable potential in the field of cancer phototherapy, primarily due to its excellent near-infrared laser absorbance and high photothermal conversion efficiency. Particularly, its derivatives, such as reduced GO (rGO), are more efficient in converting light energy into thermal energy in PTT, while also displaying superior stability (28,29). The combination of GO with polyethylene glycol (PEG) enhances biocompatibility and thermal stability, thus intensifying its photothermal effect on cancer cells (30,31). Moreover, as a photosensitizer carrier in photodynamic therapy (PDT), GO effectively delivers drugs to cancer cells or tumor tissues, reducing dosage and side effects. The combined application of GO in both PTT and PDT further enhances therapeutic outcomes (32-34). Additionally, GO-based nanocomposites, such as silver-GO and Cu_2O-GO nanocomposites, exhibit significant anticancer effects on cancer cells under light irradiation, showcasing the tremendous potential of GO as a phototherapeutic agent in cancer treatment (35-37). For instance, Hou *et al.* developed a water-dispersible Cu_2O-rGO (CRGO). The study demonstrated CRGO's selective antitumor activity under visible light using an MTT assay on HK-2, MDA-MB-231 (from human breast

adenocarcinoma), and A549 cells. Notably, HK-2 cells showed nearly 100% viability even at high CRGO doses (640 μg/mL) during the first hour of irradiation, whereas cancer cells (MDA-MB-231 and A549) experienced significant viability reduction at much lower CRGO concentrations (40 μg/mL). These findings underscore CRGO's capacity for selective cancer cell destruction under visible light exposure, with control groups maintaining near 100% viability, confirming that the observed anticancer effects were directly attributable to CRGO's light-induced activity (35).

Drug delivery

The application of GO in drug delivery has shown significant potential, largely due to its unique properties such as high surface area, good biocompatibility, and ease of surface functionalization. These characteristics make GO an ideal carrier for enhancing drug biodistribution, reducing side effects on healthy cells, improving specific selectivity, and local therapeutic absorption (23,38,39). The solubility of GO and its derivatives, like rGO, in water, and their visible and near-infrared fluorescence properties provide significant advantages for drug/gene delivery (40,41). Furthermore, these materials can be designed for controlled and intelligent drug release through external and internal stimuli-responsive systems. This enables better temporal and spatial control at lower doses, reducing toxicity and other adverse side effects. GO-based materials demonstrate vast potential in synergistically enhancing the efficiency of drug delivery.

As a potential nanocarrier, GO has been explored in drug delivery systems for oral administration, including its combination with anticancer drugs to improve bioavailability and reduce side effects. The flake-like structure and surface characteristics of GO enable effective stabilization of drugs, preventing premature escape before reaching the target. For example, curcumin encapsulated in GO-based nanoparticles and functionalized with folic acid enhances specific targeting to CRC cells (HT29), utilizing the high glutathione (GSH) concentration inside tumors to induce drug release (42). This approach increases drug absorption and efficiency in target cells while reducing the impact on normal tissues. Additionally, the development of GO-based nanoparticles includes creating intelligent drug delivery systems responsive to various stimuli, such as pH and redox conditions, enabling controlled drug release at specific sites. These systems are designed to improve the selectivity and efficiency of drug delivery while minimizing systemic side effects (43,44). Utilizing GO's unique cell uptake and recognition capabilities, researchers have developed ligands that can differentiate specific molecular receptors on cancer cell surfaces, such as folate, peptides, and monoclonal antibodies, further enhancing the targeting capabilities of the drug carriers (45,46).

Applications of GO in the diagnosis and treatment of CRC

The application of GO in biosensors and early cancer diagnosis, particularly in CRC detection, is increasing. For instance, GO-based nanocomposite biosensors have been developed for the determination of the anti-CRC drug Bevacizumab in human serum and wastewater, demonstrating its feasibility in clinical and environmental analysis (47). Additionally, leveraging GO's conductivity, researchers have created microfluidic electrochemical biosensing platforms for effectively detecting CRC exosomes, offering a rapid, economical, and efficient analytical tool with a broad detection range and low detection limit. Further, another biosensor based on GO nanocomposites can accurately measure key CRC biomarkers like carcinoembryonic antigen (CEA), showcasing high sensitivity and specificity in early cancer detection (26). Moreover, Alustiza *et al.* developed a novel non-invasive diagnostic method for CRC using magnetic GO to extract volatile organic compounds from feces, serving as a potential screening technique for CRC and precancerous lesions (48). Chen *et al.* developed a GO-based fluorescent aptasensor that provides a simple, one-step, and highly sensitive approach for the detection of mCRC cells (49). These studies highlight GO's potential in enhancing the accuracy and effectiveness of early cancer diagnosis, which is crucial for improving patient survival and treatment success rates.

GO exhibits multifaceted potential in CRC treatment. Firstly, it has been used in developing targeted drug delivery systems, such as folate-functionalized albumin/GO nanocomposites, effectively introducing curcumin and 5-fluorouracil into cancer cells (42). Lu *et al.* also developed the dual-targeting MGO-PEG-CET/DOX (MGO: magnetic GO; CET: cetuximab; DOX: doxorubicin), which could be suggested as an effective drug delivery system for anticancer therapy. It showed a 29-fold increase in therapeutic efficacy compared to the control by combining chemotherapy with PTT (50). Secondly, research by Shen *et al.* indicates that surface GO directly promotes cancer cell

autophagy and apoptosis by activating the AMPK/mTOR/ULK-1 signaling pathway (51). In phototherapy, GO-based nanocomposites can generate reactive oxygen species (ROS) under near-infrared light excitation, inducing thermotherapy and photodynamic effects to effectively inhibit tumor growth (24,32,52). Additionally, the combination of GO with anticancer drugs like doxorubicin shows significant antitumor activity by inducing apoptosis in CRC cells (53). Lastly, these studies suggest that GO and its base materials has a broad range of applications in CRC treatment, including improving drug delivery, promoting cancer cell death, and enhancing the effects of phototherapy.

Ferroptosis

Introduction to ferroptosis and its mechanisms

Ferroptosis is a novel form of regulated cell death, characterized by the accumulation of iron ions and lipid peroxidation (54). In 2012, Dixon *et al.* first discovered that the death of RAS-mutant cancer cells induced by erastin could be prevented by iron chelators and antioxidants, thereby naming it ferroptosis (55). Morphologically, ferroptosis is characterized by conspicuous shrinkage of mitochondria, increased membrane density, reduction or loss of mitochondrial cristae, and rupture of the outer mitochondrial membrane (56). This process is mediated by membrane damage catalyzed by iron-accumulated lipid peroxidation. Due to its significant regulatory role in various diseases (54,57), ferroptosis has become a research focus in recent years.

The mechanism of ferroptosis can be divided into three main pathways: iron metabolism, lipid metabolism, and the antioxidant system. These pathways are interrelated, and an imbalance in any one of them can lead to ferroptosis. Iron metabolism, an essential process in biological activities, can lead to various pathological states when iron homeostasis is disrupted. Externally, iron primarily exists in the trivalent state and is transported into cells via transferrin. Intracellular trivalent iron is reduced to divalent iron by STEAP3, which then participates in various metabolic reactions. In ferroptosis, iron's primary roles include catalyzing the non-enzymatic reaction of lipid autoxidation and serving as a cofactor for lipid peroxidase reactions (58,59).

Lipid metabolism is another key aspect of ferroptosis. Polyunsaturated fatty acids (PUFAs), prone to peroxidation, play a crucial role in ferroptosis. ACSL4 and LPCAT3 are two key enzymes involved in incorporating PUFAs into membrane phospholipids, providing "fuel" for ferroptosis. The accumulation of lipid peroxides leads to cellular membrane instability, thereby triggering cell death (57,60-62).

The antioxidant system is the third pathway regulating ferroptosis. GSH is a crucial antioxidant, while GPX4 is a key enzyme that uses GSH to reduce peroxidized lipids, preventing the accumulation of lipid peroxides. The system Xc-GSH-GPX4 pathway is an important defense line against ferroptosis. When the function of system Xc^- is inhibited, it results in reduced GSH synthesis and decreased GPX4 activity, thereby triggering ferroptosis (57,63,64).

Applications of ferroptosis in cancer research

Cancer remains one of the greatest threats to human health, with traditional treatments like chemotherapy, radiotherapy, and immunotherapy achieving limited success due to complex disease mechanisms and patient intolerance (1,65-67). Emerging research on ferroptosis suggests that exploiting this form of cell death can provide a novel anticancer therapeutic strategy, reflected in several key aspects. Firstly, ferroptosis inducers exhibit unique advantages in overcoming resistance to traditional cancer treatments, especially in drug-resistant cancer cells exhibiting epithelial-mesenchymal transition (EMT) characteristics. For instance, erastin analogs like imidazole ketone erastin (IKE) can effectively induce death in these cells, which usually show resistance to traditional chemotherapy and targeted therapies (e.g., lapatinib, erlotinib, crizotinib, dabrafenib, and vemurafenib) (68,69). Jiang *et al.* also reported inhibition of ferroptosis as a mechanism of resistance to programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy. They discovered that overexpressing Tyro3 suppresses lipid ROS triggered by erastin. However, when ferrostatin-1 (Fer-1), a ferroptosis inhibitor, prevents ferroptosis, the decrease in cell death and lipid ROS facilitated by Tyro3 overexpression does not occur (70). Secondly, ferroptosis synergizes with traditional therapies. For example, Roh *et al.* found that ferroptosis inducers can act synergistically with conventional drugs (e.g., cisplatin) to enhance therapeutic effects, demonstrating potential in suppressing tumor growth in a mouse head and neck cancer model (71). Additionally, the application of nanotechnology significantly improves the pharmacological properties of ferroptosis inducers. For instance, delivering the water-insoluble and toxic to mice withaferin A using amphiphilic, degradable, pH-sensitive nanocarriers enhanced its antitumor activity in a leukemia cell xenograft

model (72). Lastly, therapies like radiation reveal new treatment mechanisms by inducing ferroptosis. Research has found that radiotherapy can induce ferroptosis in cancer cells through ataxia-telangiectasia mutated (ATM)-mediated downregulation of SLC7A11. In certain tumor types, such as mantle cell lymphoma and prostate cancer, ATM mutations are associated with increased sensitivity to ferroptosis (73,74). These advancements indicate that ferroptosis, as a novel form of cell death, not only provides new targets and strategies in cancer treatment but also offers fresh perspectives to overcome the limitations and resistance of traditional treatments through synergistic effects with existing therapies. This suggests a more extensive and effective application in future cancer therapies.

Applications of ferroptosis in CRC research

Ferroptosis is associated with multiple signaling pathways in the treatment of CRC. For example, interferon gamma (IFNγ), in conjunction with cold plasma, triggers ferroptosis in CRC cells through the IFNγ/IFNR2/APC/TCF4/GPX4 axis (75), CAPG interference induces apoptosis and ferroptosis in colon cancer cells through the P53 pathway (76), while TRIM36 inhibition of FOXA2 plays an antitumor role in CRC by inducing NRF2/GPX4-regulated ferroptosis (77). Additionally, certain natural substances and drugs can induce or inhibit ferroptosis, thereby affecting the growth of CRC cells, such as osthole, ginsenosides, puerarin, curcumin, and andrographolide (78-82). Furthermore, concerning the application of ferroptosis mechanisms in sensitizing or overcoming resistance to traditional therapies in the treatment of CRC. Huang *et al.* demonstrated that inhibition of Nrf2 enhances the sensitivity of CRC chemotherapy by promoting ferroptosis and apoptosis (83). He *et al.* found in a CRC mouse model that butyrate induces xCT inhibition dependent on c-fos, reversing the upper ferroptosis in CRC (84). Zeng *et al.* showed that cyclin-dependent kinase 1 (CDK1) induces resistance to oxaliplatin by inhibiting ferroptosis, suggesting that CDK1 inhibitors might be an attractive strategy for treating patients with oxaliplatin-resistant CRC (85). Moreover, ferroptosis not only affects the survival of tumor cells but is also related to tumor metastasis. For instance, Lei *et al.* found that AMER1 deficiency promotes distant metastasis of CRC by inhibiting SLC7A11- and FTL-mediated ferroptosis, providing an opportunity to treat patients with mCRC harboring AMER1 mutations (86). Additionally, a recent study by Cui *et al.* found that ferroptosis plays a significant role in the influence of gut microbiota on the development and progression of CRC. They discovered that a gut microbial metabolite, trans-3-indoleacrylic acid (IDA), promotes the progression of CRC by inhibiting ferroptosis (87). Overall, ferroptosis plays multiple roles in the treatment of CRC, including directly inhibiting cancer cell growth, enhancing sensitivity to therapy, overcoming drug resistance, serving as a potential therapeutic target, and its connection with tumor metastasis. These findings provide important clues for future research and treatment strategies. Regarding the application of GO and ferroptosis in the diagnosis and treatment of CRC, we have also summarized it in a table (see *Table 2*).

Discussion

GO, a two-dimensional material with unique physicochemical properties and optical, electrical, and thermal characteristics, has shown tremendous potential in biomedical applications, particularly in cancer therapy. The high specific surface area and unique π-electron domains (aromatic ring framework and oxygen-rich surface) of GO endow it with excellent adsorption properties, allowing it to effectively bind with chemotherapy drugs, target genes, photosensitizers, etc., through π-π stacking, electrostatic interactions, and more, forming complexes for cancer diagnosis and treatment. Over the past decade, GO has made breakthrough progress as a carrier for chemotherapy drugs/target genes in tumor photothermal and PDT. However, the clinical application of GO still faces challenges such as its *in vitro* cytotoxicity, *in vitro* and *in vivo* toxicity in mammals, poor solubility in aqueous solutions, and the development of new methods for large-scale synthesis of GO. For instance, Das *et al.* treated human umbilical vein endothelial cells (HUVECs) with GO and rGO of the same size, finding that GO exhibited greater toxicity than rGO and caused severe DNA damage and a significant increase in intracellular ROS (89). Guo *et al.* discovered that exposure to GO led to significant weight loss, developmental delays, reduced mobility, and shortened lifespan in w1118 fruit flies. Further research by them suggested that this toxic effect might be related to severe damage to the fruit fly's intestine, primarily due to oxidative stress triggered by excessive accumulation of ROS (90). Rhazouani *et al.* assessed the toxicity of GO in male mice through intraperitoneal injection at different doses (2 and 5 mg/kg) over five days. While behavioral tests in mice showed no significant abnormalities, histopathological

Table 2 Graphene oxide and ferroptosis in CRC diagnosis and treatment

Type of study	Types of samples used	Main findings	Reference(s)
GO and early diagnosis	LoVo, HCT116 cell and LoVo cells in human; human blood; human fecal	Chen H *et al*. developed a GO-based fluorescent aptasensor that provides a simple, one-step, and highly sensitive approach for the detection of mCRC cells; Tao C *et al*. developed a new biosensor based on a GO nanocomposite for the precise measurement of CEA in CRC biomarker detection; Alustiza M *et al*. developed a novel non-invasive diagnostic method for CRC using magnetic GO to extract volatile organic compounds from feces, serving as a potential screening technique for CRC and precancerous lesions	(26,48,49)
GO and drug delivery systems	HUVEC, HT-29 cell; CT-26 cell and BALB/c mice	Bardania H *et al*. constructed a folic acid-modified co-delivery carrier based on graphene nanoparticles (GO-Alb-Cur-FA-5FU) to enhance the effects of 5FU and Cur on colon cancer; Lu YJ *et al*. developed the dual-targeting MGO-PEG-CET/DOX, which could be suggested as an effective drug delivery system for anticancer therapy. It showed a 29-fold increase in therapeutic efficacy compared to the control by combining chemotherapy with photothermal therapy	(42,50)
GO and phototherapy	KM12C cell	He S *et al*. developed a two-dimensional graphene oxide-template gold nanosheet (GO@SiO_2@AuNS) hybrid, which effectively killed colorectal cancer cells (KM12C) under NIR irradiation	(52)
GO promotes cancer cell death	HCT116 cell and BALB/c mice; Colon 26 cell	Shen J *et al*. discovered that GO exerts anticancer effects against CRC through ROS-dependent AMPK/mTOR/ULK-1 pathway-related autophagy and apoptosis; Krasteva N *et al*. found that exposing cancer cells to aminated graphene oxide significantly enhances cytotoxicity by inducing ROS, subsequent DNA damage, and apoptosis, thereby significantly promoting the killing of cancer cells	(51,88)
Ferroptosis triggers tumor cell death	Colorectal cancer stem cell; HCT116 cell and BALB/c mice; HCT116, SW480 cell	Lv X and others found that IFNγ is a key cytokine capable of blocking intestinal stem cells, and they verified its role in killing colorectal cancer stem cells through triggering GPX4-dependent ferroptosis; Zhao Y *et al*. discovered that both *in vitro* and *in vivo*, downregulation of CAPG can significantly inhibit CRC cells. Interfering with CAPG can block the cell cycle at the G1 phase and induce apoptosis and ferroptosis in CRC cells by upregulating the P53 pathway; Liu X et al. discovered that TRIM36-mediated FOXA2 promotes the progression of CRC by inhibiting the Nrf2/GPX4 ferroptosis signaling pathway	(75-77)
Ferroptosis and the occurrence and development of tumors	HCT8, SW480 cell; MC38 3D tumour spheroids and HT29 organoids	Lei S *et al*. discovered that the loss of AMER1 promotes distant metastasis of CRC by inhibiting iron death mediated by SLC7A11 and FTL; Cui W *et al*. discovered that a gut microbiota metabolite, IDA, promotes the progression of CRC by inhibiting ferroptosis	(86,87)
Ferroptosis and drug resistance	HCT116, SW480, Hep3b cell and BALB/c mice; HCT8, HT29 cell	He Y *et al*. discovered that butyrate reverses ferroptosis resistance in CRC by inducing c-Fos-dependent suppression of xCT; Zeng K *et al*. discovered that CDK1 inhibitors may be an attractive strategy for treating oxaliplatin-resistant CRC patients	(84,85)

CRC, colorectal cancer; GO, graphene oxide; mCRC, metastatic colorectal cancer; CEA, carcinoembryonic antigen; Alb, albumin; Cur, curcumin; FA, folic acid; 5FU, 5-fluorouracil; MGO, magnetic graphene oxide; PEG, polyethylene glycol; CET, cetuximab; DOX, doxorubicin; NIR, near-infrared; ROS, reactive oxygen species; CAPG, capping actin protein; FOXA2, forkhead box transcription factor A2; IDA, trans-3-indoleacrylic acid; CDK1, cyclin-dependent kinase 1.

analysis of liver sections indicated that GO caused liver inflammation (91). Additionally, Liao *et al.* studied the cytotoxicity of graphene and GO (350 nm) on the normal components of human red blood cells, finding that severe hemolysis was the result of strong electrostatic interactions between the red blood cell membrane lipid bilayer and the graphene surface, leading to membrane disruption (92). These findings underscore the need for further research to address issues related to the toxicity and biocompatibility of GO before its clinical translation can be advanced.

Simultaneously, ferroptosis, as a novel form of non-apoptotic cell death, offers a new perspective in cancer therapy. Particularly for cancers like CRC that develop resistance to traditional treatments, research on ferroptosis not only aids in overcoming resistance issues but may also enhance treatment effectiveness. Future studies will continue to deepen the understanding of ferroptosis mechanisms and identify more effective ferroptosis inducers for clinical cancer treatment. Although significant progress has been made in studying ferroptosis in tumor therapy, it is still in its early stages, mainly focusing on basic research. The mechanisms linking ferroptosis and CRC are still unclear and require further investigation and validation. Currently, research on the role of ferroptosis mechanisms in the occurrence and development of CRC remains insufficient, and the complex mechanisms linking ferroptosis with CRC are not yet clear. Therefore, there is an urgent need for comprehensive research and validation to elucidate how ferroptosis affects the pathogenesis of CRC. This includes a deeper understanding of the cellular and molecular pathways of ferroptosis in CRC, identifying potential biomarkers for early detection, and exploring how ferroptosis can be used as a therapeutic intervention for CRC. Additionally, research should aim to identify which CRC patients are most likely to benefit from treatments related to the ferroptosis mechanism and to determine biomarkers that can be used for efficacy assessment and monitoring. The ultimate goal of research is clinical translation to benefit patients, improving patient treatment outcomes, and enhancing quality of life. Although the path is long and fraught with challenges, through in-depth research and innovation, we can progress toward this goal.

In summary, the application prospects of GO and ferroptosis in cancer therapy are vast. Despite the need to overcome numerous challenges, the rapid development of nanomaterial science, particularly the advancements in GO and its substrates, has turned many impossibilities into possibilities, especially in cancer diagnosis and treatment. Furthermore, it's worth mentioning that combining GO with ferroptosis-inducing therapies presents an intriguing path that remains largely unexplored. In the future, GO could be further modified to directly influence the proliferation, migration, and invasion of tumor cells, such as those in CRC, through mechanisms like ferroptosis. Additionally, research into GO's drug-carrying and releasing capabilities could be expanded to include ferroptosis inducers, utilizing GO's delivery potential to enhance ferroptosis induction in cancer cells. Moreover, addressing the toxicity of GO and improving its biocompatibility is crucial for its effective integration into cancer therapy. In summary, while GO and the ferroptosis mechanism offer significant opportunities to advance cancer treatment, their integration necessitates a thorough understanding of their interactions, meticulous management of potential toxicities, and innovative strategies to leverage their combined potential to improve cancer treatment outcomes. This area warrants further research and exploration by the scientific community.

Conclusions

This review underscores the potential of GO and ferroptosis in advancing cancer therapy, particularly for CRC. Despite various challenges, the integration of GO and ferroptosis mechanisms holds substantial promise for enhancing cancer treatment efficacy, warranting further research and development.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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