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MMP-Responsive PEGylated Graphene Oxide Nanocarriers for miRNA Delivery in Colorectal Cancer

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Abstract

Colorectal cancer is one of the major causes of morbidity and mortality in cancer patients globally, and there is an immediate need to develop more specific and effective treatment methods. mRNA-based therapeutics have become promising molecular interventions because they can regulate multiple oncogenic pathways, but poor stability, rapid degradation, off-target effects, and inefficient tumor delivery are limitations to their clinical translation. PEGylated, matrix metalloproteinase-responsive graphene oxide nanocarriers are the new generation of enzyme-directed delivery platforms capable of bypassing those barriers. Graphene oxide provides a high loading capacity and protection for miRNA, and PEGylation increases systemic stability, biocompatibility, and extended circulation via stealth effects. PEG shedding and focal release of miRNA are triggered by the incorporation of matrix metalloproteinase-cleavable peptide linkers, resulting in tumor-selective activation due to the high matrix metalloproteinase-2/9 levels in the colorectal tumor microenvironment. After cellular uptake and endosomal escape, transferred miRNAs bind the RNA-induced silencing complex to execute sequence-specific gene silencing, thereby inducing apoptosis, suppressing proliferation and metastasis, and sensitizing to chemotherapy. This review highlights the present-day design strategies, biological processes, preclinical success, co-delivery methods, and translational issues of matrix metalloproteinase-sensitive GO-PEG miRNA systems. Together, these intelligent nanocarriers provide a potential nanomedicine platform for targeted therapy in CRC.

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1. Introduction

Colorectal cancer (CRC) is a significant health burden in the world, as it is one of the most frequently diagnosed cancers and the primary cause of cancer-related deaths in most countries, with the aged population and westernized food habits as well as sedentary lifestyles leading to increased incidence of this condition worldwide [1]. Even with advanced screening and multimodal management, a considerable number of patients are diagnosed at late stages, and the prognosis is unfavorable. Existing treatment measures, such as surgical resection, cytotoxic chemotherapy (e.g., FOLFOX, FOLFIRI), targeted biologics targeting the VEGF/EGFR pathways, and immune checkpoint inhibitors, have improved survival but are constrained by various limitations [2]. Event protein heterogeneity in tumors, inborn and acquired drug resistance, dose-limiting toxicity, and the inability to offer targeted and immunotherapies (especially the limited efficacy of immunotherapy in microsatellite-stable tumors) are barriers to sustained treatment responses. Also, treatment costs are high, and access to molecular diagnostics is limited, which also worsens the outcome disparities, especially in low- and middle-income areas. All these problems indicate an immediate need to develop more specific oncology strategies, new biomarkers, and combination-based therapies to overcome therapeutic resistance and reduce CRC-related morbidity and mortality [3], [4].

The development of microRNA (miRNA)-based therapeutics is a promising new frontier in the management of colorectal cancer (CRC) owing to miRNAs' critical roles in tumor initiation, progression, metastasis, and resistance to therapy. miRNAs are post-transcriptional regulators of gene expression (small, non-coding RNA molecules: 1825 nucleotides) that can regulate key oncogenic and tumor suppressor pathways, including Wnt/ -catenin, PI3 Dysregulation of certain miRNAs such as oncogenic miRNAs (oncomiRs) such as miR-21 and miR-155, and tumor-suppressive miRNAs, such as miR-34a, miR-143, and miR-145, have been strongly associated with proliferation, invasion, immune evasion, and chemoresistance in CRC [5]. Two major approaches have been developed: miRNA mimics, which replace tumor-suppressor miRNAs, and anti-miRNA oligonucleotides (antagomiRs), which silence oncogenic miRNAs. Preclinical evidence shows that miRNA modulation can sensitize CRC cells to chemotherapy, inhibit metastasis, and reduce tumor growth. Nevertheless, clinical translation has been associated with problems such as delivery instability, off-target effects, immune stimulation, and tumor-specific targeting. The development of nanoparticle delivery systems, viral vectors, lipid-based delivery systems, and exosome-mediated transport is now being investigated to augment the precision and bioavailability of these therapies. Together, miRNA-based therapeutics have significant potential as next-generation precision medicine therapeutics for CRC, which may be used as a single therapy option or integrated with existing chemotherapy and immunotherapy regimens [6].

The barriers to the clinical translation of miRNA-based therapeutics in solid tumours, such as colorectal cancer, remain delivery-related. MiRNAs administered systemically, either as mimics or inhibitors, are rapidly degraded by circulating nucleases, cleared, opsonized by serum proteins, and exhibit low bioavailability and a short half-life. Biological barriers to efficient tumor accumulation include abnormal tumor vasculature, high interstitial fluid pressure, and dense extracellular matrix, which limit nanoparticles' extravasation and intratumor penetration even with chemical stabilization. Cellular uptake is also a challenge, as negatively charged miRNA molecules are relatively impermeable to the membrane and accumulate in endosomes, leading to lysosomal degradation rather than cytoplasmic release, where gene silencing occurs [7]. Non-specific biodistribution increases the risk of off-target gene modulation and systemic toxicity, whereas activation of the innate immune response via Toll-like receptors may lead to inflammatory effects. Mixed receptor expression and tumor heterogeneity complicate targeted delivery. All of these physicochemical, biological, and immunological barriers imply that the advanced delivery platforms, lipid nanoparticles, polymeric carriers, viral vectors, and exosome-based systems are necessary to improve stability, tumor targeting, endosomal escape, and therapeutic effectiveness of miRNA interventions in solid malignancies [8], [9].

The idea of enzyme-responsive nanocarriers for cancer therapy, especially for miRNA delivery in solid tumors such as colorectal cancer, is motivated by the need for spatiotemporal control of drug release in the tumor microenvironment (TME) and reduced systemic toxicity. Abnormal upregulation of certain enzymes, such as matrix metalloproteinases (MMP-2, MMP-9), hyaluronidase, cathepsins, o-glucuronidase, and phospholipases, is observed in solid tumors and is important for extracellular matrix remodeling, invasion, and metastasis [10]. Nanocarriers that are enzyme-responsive take advantage of this biochemical marker to incorporate cleavable linkers, degradable coatings, or enzyme-substrate patterns that are resistant to degradation in circulation but are selectively degraded by tumor-associated enzymes [11]. This induces site-selective cargo discharge, increasing intratumoral retention and cellular uptake of therapeutic payloads, including, but not limited to, miRNA mimics or antagomiRs. Also, enzymatic degradation may be used to enhance tumor invasion by breaking the barriers of the extracellular matrix, shrinking nanoparticle size, or reversing charge. Such systems enhance pharmacokinetics, protect miRNAs from enzymatic degradation, and reduce off-target exposure. Notably, enzyme responsiveness may also be combined with multi-stimuli designs (pH, redox, hypoxia) to increase control in delivery precision [12].

PEGylated graphene oxide (GO) as a matrix metalloproteinase (MMP)-responsive nanoplatform has emerged as an excellent option for miRNA delivery into solid tumors, combining tumor responsiveness with improved systemic stability and nucleic acid loading capacity. The MMPs, especially MMP-2 and MMP-9, are highly expressed in the microenvironment of colorectal tumors and play key roles in extracellular matrix degradation, invasion, and metastasis; therefore, they are the most effective biological triggers for site-selective drug delivery [11]. Graphene oxide is a two-dimensional and high surface area scaffold enriched with oxygen-containing functional groups that allow efficient adsorption or conjugation of miRNAs through π π and hydrogen bonding, as well as electrostatic interactions, and protect them against degradation by nuclease. PEGylation also increases biocompatibility, gives the systemic circulation a longer lifetime, decreases opsonization and reticuloendothelial clearance, and enhances passive tumor accumulation through the increased permeability and reticuloendothelial clearance effect (EPR) [13]. MMP-cleavable peptide linkers or coatings can be incorporated to enable the nanocarrier to remain stable in circulation while degrading in the tumor microenvironment, triggering localized payload release and allowing deeper tumor penetration. Also, cellular uptake and endosomal escape via PEG shedding can be achieved through enzyme-mediated cleavage of PEG, thereby exposing graphene oxide. The spatiotemporally regulated delivery method reduces the off-target toxicity and maximizes intratumor miRNA bioavailability. Combined, MMP-

responsive PEGylated GO offers tumor selectivity, high loading capacity, protection of labile nucleic acids, and controlled release, making it one of the most promising solutions for overcoming delivery barriers to miRNA-based colorectal cancer therapeutics [14].

2. Matrix Metalloproteinases in Colorectal Cancer

The large family of endopeptidases includes matrix metalloproteinases (MMPs), which are essential for remodeling the extracellular matrix (ECM) during physiological and pathological conditions, including colorectal cancer (CRC). More than 20 human MMPs have been discovered to date, and are widely grouped by substrate specificity and structural characteristics in collagenases (e.g., MMP-1, MMP-8, MMP-13); gelatinases, MMP-2, MMP-9); stromelysins, e.g., MMP-7, MMP-26); membrane-type MMPs, e.g., MMP-14/MT1-MMP); and so on. Structurally, most MMPs have regions of conservation comprising a propeptide region, which maintains enzyme latency, a catalytic zinc-binding domain, a hinge region, and a hemopexin-like domain, which confer substrate specificity and protein-protein interactions [15]. MMP activity is also highly regulated at several levels: transcriptional control, activation of zymogens, and inhibition by endogenous tissue inhibitors of metalloproteinases (TIMPs). In CRC, the dysregulation of certain MMPs, specifically MMP-2, MMP-7, MMP-9, and MT1-MMP, has been strongly implicated in tumor invasion, tumor angiogenesis, tumor metastasis, and poor prognosis by degrading basement membranes and stromal ECMs such as collagen, laminin, and fibronectin. In addition to structural remodelling, MMPs also regulate the bioactive molecules, such as growth factors, cytokines, and chemokines, thus defining the tumor microenvironment. This highly complex functional signature makes the MMP family both important agents in CRC pathogenesis and highly interesting targets for diagnostic and therapeutic interventions [16].

The most clinically and biologically interesting proteolytic enzymes involved in colorectal cancer (CRC) development include matrix metalloproteinases MMP-2, MMP-7, and MMP-9, owing to their key roles in extracellular matrix (ECM) degradation, tumor invasion, tumor metastasis, and regulation of the tumor microenvironment. MMP-2 (gelatinase A) and MMP-9 (gelatinase B) primarily degrade type IV collagen, a major component of the basement membrane, facilitating early invasion and intravasation of tumor cells [17]. The overexpression of MMP-2 in CRC has been associated with high tumor stage, lymph node metastasis, and lower overall survival. On the same note, high levels of MMP-9 are closely associated with aggressive phenotypes, angiogenesis, and inflammatory remodeling of the microenvironment, as MMP-9 releases vascular endothelial growth factor (VEGF) and other angiogenic growth factors. In comparison, MMP-7 (matrilysin), which is one of the smallest MMPs and lacks the hemopexin domain, is exclusively synthesized by tumor epithelial cells but not stromal elements. MMP-7 enhances CRC progression by degrading a wide array of substrates, including laminin, fibronectin, E-cadherin, and proteoglycans, thereby stimulating epithelial-mesenchymal transition (EMT), loss of cell adhesion, and metastatic spread. It also triggers other pro-MMPs and processes bioactive molecules, including Fas ligand and pro-tumor necrosis factor-alpha, thereby enhancing tumorigenic signaling. Together, deregulated expression of MMP-2, MMP-7, and MMP-9 not only contributes to the invasion and metastasis of CRC but also to its poor prognosis, making them useful biomarkers and appealing targets for enzyme-responsive therapeutic and nanodelivery systems [17].

The invasion, metastasis, and extracellular matrix (ECM) remodelling that occur in colorectal cancer (CRC) rely on the coordinated proteolytic degradation of structural and regulatory elements of the tumor microenvironment by matrix metalloproteinases (MMPs). During tumor invasion, MMPs, including MMP-2 and MMP-9, degrade type IV collagen and laminin in the basement membrane, thereby breaking down the physical barriers that limit the movement of epithelial cells and facilitating the invasion of malignant cells into surrounding stromal tissues [18]. At the same time, MMP-7 and membrane-type MMPs degrade adhesion molecules, such as E-cadherin, promoting epithelial-mesenchymal transition (EMT), cell-cell disintegration, and increased migratory ability. The MMP activity contributes to intravasation by destabilizing vascular basement membranes, facilitating extravasation at the secondary tumor site and at distant sites, thereby promoting secondary tumor colonization in the metastatic cascade [19]. Along with structural degradation, MMP-mediated ECM remodeling liberates and activates sequestered growth factors, including VEGF, TGF-2, and fibroblast growth factors, thereby promoting angiogenesis, tumor growth, and stromal recruitment. Chemokines and cytokines are further proteolytically processed to create a pro-inflammatory, immunomodulatory microenvironment favorable to tumor progression. Together, during ECM disassembly, MMPs modulate cell adhesion, activate pro-tumorigenic signaling molecules, and facilitate vascular dissemination, thereby playing an important role as molecular drivers of CRC invasiveness and metastatic competence [20].

Due to the aberrant overexpression and proteolytic activity of matrix metalloproteinases (MMPs) in the tumor microenvironment (TME), these biological triggers have attracted significant attention for targeted drug and miRNA delivery in colorectal cancer (CRC). Enzymes MMP-2, MMP-7, and MMP-9 are highly expressed in invasive and metastatic CRC tissues and are directly involved in the destruction of the extracellular matrix and stromal remodeling [21]. This tumor-specific enzyme profile will provide an endogenous stimulus that can be exploited to activate

therapeutic sites. MMP-responsive delivery systems are typically designed with cleavable peptide linkers, a degradable polymer coating, or enzyme-sensitive gatekeepers that remain intact during systemic circulation but are cleaved upon reaching tumor-targeted areas, where MMP concentrations are high. This enzymatic degradation-induced controlled release of encapsulated payloads, such as chemotherapeutics, siRNA, or miRNA mimics/antagomiRs, directly in the tumor environment achieves local increases in drug bioavailability and reductions in off-target toxicity [22]. Also, MMP-mediated cleavage may reduce nanoparticle size, reverse charge, or shed polyethylene glycol (PEG), thereby enhancing tumor penetration and cellular uptake. These types of bioresponsive systems are compatible with therapeutic activation in line with disease pathology and provide spatiotemporal control in the delivery of nucleic acids. Subsequently, exploiting MMPs as endogenous biological stimuli is a logical, highly selective approach to overcome delivery barriers and enhance the therapeutic effects of miRNA-based interventions in CRC [23].

3. miRNA Dysregulation and Therapeutic Targets in CRC

Elevated MicroRNA (miRNA) expression is one of the characteristics of the pathogenesis of colorectal cancer (CRC), and with the help of its functional classes, they were distinguished into tumor-suppressor miRNAs and oncogenic miRNAs (oncomiRs) on the basis of their gene regulatory activity [24]. Tumor-suppressor miRNAs are generally downregulated in CRC and play a role in preventing malignant transformation by inhibiting oncogenes, oncogenic cell-cycle drivers, and pro-metastatic pathways. For example, miR-34a, a transcriptional target of p53, represses proliferation and apoptosis by targeting BCL2, MET, and CDK6, whereas miR-143 and miR-145 prevent KRAS signaling, cytoskeletal remodelling, and tumor development. The depletion of these miRNAs contributes to uncontrolled proliferation, invasion, and resistance to therapy. Oncogenic miRNAs, on the other hand, are often overexpressed and contribute to tumorigenesis by suppressing tumor-suppressor genes and promoting proliferation, invasion, and resistance to chemotherapy [25]. miR-21, one of the most well-researched oncomiRNAs in cancer, inhibits PTEN, PDCD4, and TPM1. On the same note, miR-155 and the miR-17-92 cluster induce tumorigenesis, angiogenesis, and immune escape, all of which are associated with inflammation. The dynamic imbalance between tumor-suppressive and oncogenic miRNAs destabilizes key signaling pathways, such as the Wnt/β-catenin, PI3K/AKT, TGF-β-catenin, and EGFR pathways, that promote the initiation and progression of CRC. This dichotomy has therapeutic implications for a dual-pronged intervention: restoring downregulated tumor-suppressor miRNAs with synthetic mimics and inhibiting overexpressed oncomiRs with antagomiRs or locked nucleic acid (LNA) inhibitors, making miRNA modulation a precision approach in the management of CRC [26].

The most important microRNAs (miRNAs) in colorectal cancer (CRC) development form a complex regulatory network that controls tumor growth, invasion, metastasis, angiogenesis, and resistance to therapy. miR-21 is one of the most notable oncogenic miRNAs, consistently overexpressed and promoting tumor growth and chemoresistance by targeting tumor suppressors such as PTEN and PDCD4. miR-17-92 cluster promotes proliferation and angiogenesis by regulating E2F transcription factors and PI3K/AKT, miR-155 promotes inflammation-induced tumorigenesis and immune evasion, and miR-31 promotes invasion and metastatic spread by regulating Rho/EMT-related pathways [27]. On the other hand, miR-34a, which is a p53-regulated miRNA, reduces apoptosis and cell-cycle arrest by inhibiting BCL2 and CDK6 and prevents metastasis by inhibiting epithelial-mesenchymal transition (EMT) via ZEB1/ZEB2 inhibition. miR-200 family members suppress oncogenes of the RAS family and stemness-like pathways, whereas a number of tumor-suppressor miRNAs are often silenced in CCR progression. miR-135b facilitates the activation of Wnt/β-catenin through APC repression, and miR-224 has been associated with advanced tumor stages and poor prognosis. The overall impact of the dysregulation of these key miRNAs is their ability to disrupt central oncogenic pathways, such as Wnt/ 0 -catenin, EGFR, TGF-β -, and PI3K/ AKT, to promote the progression of CRC, and as such, they serve as diagnostic biomarkers and indicators of their role as therapeutic targets [28], [29].

The therapeutic principles of miRNA replacement and miRNA inhibition in CRC rely on the central role of miRNA dysregulation in promoting tumor development, progression, metastasis, and resistance to therapy, such as the downregulation of miR-34a, miR-143, and miR-145 that suppresses the expression of oncogenes, contributes to intense tumor growth, and inhibits tumor apoptosis. Synthetic miRNA mimics can be delivered to restore post-transcriptional repression of essential oncogenic targets (e.g., KRAS, BCL2, CDK6), suppress tumor growth, trigger cell-cycle arrest, and increase cancer cells ' response to chemotherapy and radiotherapy [30]. On the other hand, miRNA inhibition therapy targets overexpressed oncogenic miRNAs (oncomiRs), such as miR-21, miR-155, and the miR-17-92 cluster, which stimulate invasion, angiogenesis, immune evasion, and drug resistance by silencing tumor suppressor genes, including PTEN and PDCD4. The rationale of this approach is to selectively inhibit the activity of oncomiRs using antisense oligonucleotides, antagomiRs, locked nucleic acid (LNA) inhibitors, or miRNA sponges [31]. The combination of these complementary technologies offers a dual-modality precision medicine system that can be used to normalize tumor suppression or block oncogenic drivers, and to concurrently regulate multiple downstream targets in dysregulated signaling networks, including Wnt/β-catenin, PI3K/AKT, and TGF-β. Based on these facts, miRNA replacement and inhibition as a therapeutic approach to CRC is a mechanistically sound and

highly versatile approach, especially when combined with sophisticated nanocarrier delivery systems [32].

Table 1 summarizes key microRNAs that play crucial roles in the initiation, progression, and metastasis of colorectal cancer. It highlights both oncogenic miRNAs (oncomiRs) that promote tumour growth and tumour-suppressor miRNAs that inhibit cancer development. The table also outlines their molecular targets and the signalling pathways they regulate. In addition, it emphasizes their value as diagnostic and prognostic biomarkers. Overall, the table underscores the therapeutic potential of miRNA-based strategies, including miRNA mimics and inhibitors, in colorectal cancer management [33], [34].

Table 1: miRNAs Involved in Colorectal Cancer and Their Therapeutic Significance

S. No.	miRNA	Expression Pattern in CRC	Key Molecular Targets	Therapeutic Role	Reference
1.	miR-21	Upregulated	PTEN, PDCD4, TPM1	OncomiR inhibition target	[35], [36]
2.	miR-155	Upregulated	SOCS1, FOXO3a	Anti-miR therapy	[37]
3.	miR-17	Upregulated	E2F1, PTEN	Proliferation suppression via inhibition	[38]
4.	miR-18a	Upregulated	ATM	OncomiR inhibition	[39], [40]
5.	miR-19a/b	Upregulated	PTEN, BIM	Anti-miR strategy	[41]
6.	miR-20a	Upregulated	SMAD4, E2F1	Metastasis inhibition target	[42]
7.	miR-31	Upregulated	RASA1	Anti-metastatic inhibition	[43], [44]
8.	miR-92a	Upregulated	PTEN, KLF4	Angiogenesis inhibition	[45], [46]
9.	miR-135b	Upregulated	APC	Wnt pathway targeting	[47]
10.	miR-224	Upregulated	PHLPP1, SMAD4	Prognostic & inhibition target	[48]
11.	miR-301a	Upregulated	TGFBR2	Anti-invasive therapy	[49]
12.	miR-429	Upregulated	SOX2 modulators	EMT targeting	[50], [51]
13.	miR-7	Downregulated	EGFR, RAF1	Replacement therapy	[52]
14.	miR-9	Downregulated	CXCR4	Anti-metastatic replacement	[53]
15.	miR-22	Downregulated	MYCBP, Sp1	Tumor suppression restoration	[54], [55]
16.	miR-26a	Downregulated	EZH2, CCND2	Cell-cycle inhibition	[56], [57]
17.	miR-29b	Downregulated	MCL1, DNMT3B	Apoptosis induction	[58], [59]
18.	miR-34a	Downregulated	BCL2, MET, CDK6	p53-linked replacement	[60]
19.	miR-124	Downregulated	STAT3	Anti-proliferative replacement	[61]
20.	miR-133a	Downregulated	FSCN1	Anti-invasion therapy	[62], [63]
21.	miR-137	Downregulated	CDC42	EMT suppression	[64]

22.	miR-139-5p	Downregulated	NOTCH1	Metastasis inhibition	[65], [66]
23.	miR-143	Downregulated	KRAS	Replacement therapy	[67]
24.	miR-145	Downregulated	IRS1, SOX2	Stemness inhibition	[68], [69]
25.	miR-148a	Downregulated	DNMT1	Epigenetic modulation	[70], [71]
26.	miR-152	Downregulated	IGF1R	Anti-proliferative	[72]

4. Graphene Oxide as a Nanocarrier for miRNA Delivery

Since GO has a distinct structural architecture and tunable surface chemistry that facilitate efficient loading of nucleic acids, their protection, and intracellular delivery, it has demonstrated itself as a highly versatile nanocarrier for miRNA. Structurally, GO is a two-dimensional, single- to few-layered carbon nanomaterial derived from graphite, with a high specific surface area and a planar sp 2 - hybridized carbon lattice, and high levels of oxygen-containing functional groups, including hydroxyl, epoxide, carbonyl, and carboxyl [73]. These functional groups are asymmetrically positioned on the edges and basal plane, giving the group hydrophilicity, colloidal stability, and easy chemical modification. The longer π-conjugated domains allow π-π stacking interactions with nucleobases, and electrostatic interactions and hydrogen bonding facilitate the adsorption or conjugation of the negatively charged miRNAs in large quantities, preventing enzymatic degradation [74]. Further increase of biocompatibility, dispersion stability, and tumor-specific targeting, and less aggregation and non-specific protein adsorption by surface functionalization with polyethylene glycol (PEG), polyethyleneimine (PEI), chitosan, or targeting ligands [75]. Also, GO's sheet-like morphology is ultrathin, facilitating cellular membrane interactions and endocytosis. Theranostic integration is also possible due to its inherent photothermal and imaging capabilities. Together, the structural integrity, large surface area, and chemically addressable functional groups of graphene oxide render it an extraordinarily versatile platform for engineered, stimuli-responsive miRNA nanodelivery systems in colorectal cancer therapeutics [76].

Noncovalent physicochemical interactions, especially π-deprotonated stacking and electrostatic attraction between the two, are the primary mechanisms that dictate efficient loading of miRNA onto GO nanocarriers and maintain miRNA structural integrity and bioactivity. Such 2D π-electron arrays are oriented through van der Waals forces, as a result of which the miRNA molecules adsorb onto the GO surface in a stable and reversible fashion [77]. This interaction not only allows nucleic acid thickening but also protects miRNA from nuclease-mediated degradation in the system. To supplement this, the electrostatic interactions are vital, especially when GO is functionalized with cationic polymers, e.g., polyethyleneimine (PEI), chitosan, or any amine-based functional group. Because the negatively charged phosphate backbone of miRNAs has a high affinity to positively charged surfaces through ionic attraction, loading efficiency and stability of the complexes are improved. This condensation is also facilitated by charge, enhancing cellular uptake by promoting interaction with negatively charged cell membranes [78]. Notably, these noncovalent loading techniques allow controlled release in the intracellular environment, where alterations in pH, enzymatic activity, or ionic strength can disrupt interactions with the miRNA, leading to its dissociation. Combined, π- π stacking with electrostatic binding offers synergistic, high-efficiency loading of GO, upon which the potential of GO to deliver miRNA in colorectal cancer treatment is based [79].

There are several key advantages of pristine GO as a nanocarrier for miRNA delivery in colorectal cancer, owing to its specific physicochemical/biological characteristics. It has a high two-dimensional specific surface area, owing to its sheet-like structure, enabling high-density loading of nucleic acids via π-π stacking and hydrogen bonding. The presence of oxygen-containing functional groups, including hydroxyl, carboxyl, and epoxide groups, provides inherent hydrophilicity and enables facile chemical functionalization with polymers, targeting ligands, or stimuli-responsive linkers [80]. This adjustability can be used to control dispersibility, biocompatibility, and tumor localization specifically. Also, GO can shield adsorbed miRNAs from nuclease degradation and early systemic clearance. It has an ultrathin morphology that facilitates efficient endocytosis-mediated cellular uptake, as well as natural photothermal and imaging properties that enable theranostics [81]. Although these are the benefits, pristine GO has a series of limitations that inherently limit direct clinical translation. Untouched GO surfaces may cause dose-dependent cytotoxicity, oxidative stress, membrane damage, and inflammatory responses, driven by sharp sheet edges and the production of reactive oxygen species (ROS). Biodistribution can be impaired and delivery efficiency reduced by poor physiological stability and the compound's tendency to aggregate in salt- or protein-rich biological fluids [82].

5. PEGylation of Graphene Oxide: Design and Functional Advantages

PEGylation of GO is an important surface-engineering approach that enhances nanocarrier biocompatibility, colloidal stability, and systemic delivery of miRNA in colorectal cancer. PEGylation is performed by covalent or noncovalent attachment of hydrophilic PEG chains to oxygen-reactive functional groups on the GO surface, which form a steric hydration corona that regulates nano-bio interactions. PEGylation using covalent techniques is most common and involves the formation of amide or ester bonds, exploiting the carboxyl groups of GO via carbodiimide chemistry (e.g., EDC/NHS conjugation to amine-terminated PEG, PEG-NH2) [83]. Alternatively, nucleophilic reactions can be carried out on hydroxyl or epoxide groups of GO by reacting with PEG derivatives or by ring-opening reaction. PEG with thiol groups can also be grafted using the linker-mediated methods. Strong PEG anchoring is the result of covalent attachment, which limits the desorption of PEG in circulation [84]. Conversely, noncovalent PEGylation is based on hydrophobic interactions, hydrogen bonding, or π-- stacking with amphiphilic PEGylated surfactants, phospholipid-PEG conjugates, or pyrene-PEG linkers, which adsorb onto the GO basal plane but do not modify its carbon lattice. Noncovalent coatings are easier to make but can be less stable in the long term [85]. More complex PEGylation constructs are heterobifunctional PEGs (e.g., PEG-maleimide, PEG-folate, PEG-RGD) that enable concurrent active tumor targeting and stealth shielding. Moreover, cleavable PEG linkers, which are responsive to enzymes (MMPs), pH, or redox gradients, are also being used to enable PEG shedding in the tumor microenvironment, thereby resuming cellular uptake. Together, PEGylation chemistry offers a platform for modularity to maximize GO dispersibility, extend blood circulation, and reduce immunogenicity, as well as multifunctionalization of miRNA nanodelivery with precision [86].

PEGylation significantly impacts the physicochemical and biological functions of GO nanocarriers, including enhanced colloidal stability, biocompatibility, and systemic circulation time, all of which contribute to the successful delivery of miRNA in colorectal cancer [87]. Colloidally, the functionalization of the GO surface with hydrophilic polyethylene glycol (PEG) yields a thick hydration shell that provides steric repulsion and suppresses van der Waals aggregation, at least under physiological salt and protein concentrations [88]. This steric stabilization enhances aqueous dispersibility, prevents sheet stacking, and maintains nanoscale size distribution, thus enabling even biodistribution and tumor accumulation. PEGylation of pristine GO covers reactive oxygen-containing groups and sharp edges, which are known to cause significant membrane damage, oxidative stress, hemolysis, and inflammatory immune responses [89]. The stealth property of PEG is also used to reduce nonspecific protein adsorption (opsonization), thereby reducing macrophage and reticuloendothelial system (RES) recognition. PEGylated GO, therefore, has a significantly extended blood circulation half-life than unmodified GO, allowing increased exploitation of the augmented permeability and retention (EPR) effect to passively tumor targeting [90]. Long-term systemic persistence enhances the likelihood of tumor extravasation and intracellular delivery of miRNA cargo. PEGylation, as a group, can convert a potentially reactive nanomaterial into a physiologically stable, hemocompatible, and long-circulating delivery system for systemic nucleic acid therapy [91].

PEGylated GO nanocarriers are important design parameters for miRNA therapeutics, as their physicochemical behaviour and biological interactions depend on PEG density and molecular weight. PEG density refers to the number of PEG chains of the surface grafting coverage of GO, and it has a direct impact on steric stabilization, protein adsorption, and cellular interactions [92]. A dense hydration corona is formed by a high PEG surface density, which increases colloidal stability, limits aggregation, confers high PEG with good stealth properties by reducing opsonization and macrophage uptake, and increases systemic circulation. Nonetheless, over PEGylation may prevent internalization and evasion into endosomes of cells by concealing the cell membrane charge and interfering with cell membrane-cell membrane interactions- a process commonly referred to as the PEG dilemma. On the other hand, low PEG densities can enhance cellular uptake at the expense of stability and immune recognition [93].

PEG molecular weight (MW) also regulates the effect of nanocarriers. PEG (e.g., 12kDa) is less sterically protective and does not circulate as long, but peptides with higher molecular weight (e.g., 5–20 kDa) form thicker hydration layers that prolong blood half-life, decrease renal elimination, and increase tumor accumulation through the enhanced permeability and retention (EPR) effect [94]. However, extremely high-MW PEG can increase hydrodynamic volume, decrease tumor invasiveness, and impede intracellular delivery of miRNA cargo. Thus, in general, an ideal design is a compromise between PEG chain length and grafting density to achieve adequate stealth and stability without compromising tumor uptake or intracellular delivery. More sophisticated systems now use cleavable or stimuli-responsive PEG linkages to retain the circulation advantages while allowing PEG shedding in the tumor microenvironment [93].

PEG has dual functions in the graphene oxide (GO)-based nanocarrier: it serves as a bioprotective coating during systemic circulation and facilitates the release of therapeutic cargo (miRNAs) in the tumor microenvironment. Surface-grafted PEG chains act as a shielding moiety in the form of a hydrated steric coat of the nanocarrier, effectively covering the underlying GO surface charge, reactive functional groups, and sharp edges [95]. This stealth corona reduces nonspecific adsorption of proteins (opsonization), decreases recognition and clearance by the mononuclear phagocyte/reticuloendothelial

system, and reduces immune activation, hemolysis, and oxidative stress. Therefore, PEGylated nanocarriers exhibit prolonged blood circulation, improved physiological stability, and enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect [96]. In addition to passive protection, PEG is also involved in controlled, stimuli-responsive release processes. PEG may serve as a removable gatekeeper, forming cleavable links or enzyme-sensitive peptide spacers in the presence of GO, thereby stabilizing the nanocarrier in circulation but selectively shedding it in the tumor microenvironment. PEG linkers are cleaved by matrix metalloproteinases (MMPs) or acidic pH or redox gradients to reveal the underlying GO surface, which repolarizes positively (when cationic coats are present), and facilitates uptake by cells and endosomal escape. PEG dislocation can also destabilize miRNA-binding interactions, releasing the payload at the disease site. PEG is therefore not just a protective stealth group, but also a programmable regulatory unit that controls nanocarrier activation and miRNA release in response to tumor-specific biological signals, thereby increasing in vivo therapeutic specificity and reducing off-target toxicity [97].

6. MMP-Responsive Design Strategies for GO-PEG Nanocarriers

The strategies for matrix metalloproteinase (MMP)-responsive design of GO-PEG nanocarriers depend heavily on the integration of enzyme-cleavable peptide linkers, which facilitate tumor-selective activation and regulated miRNA release in the colorectal cancer microenvironment. Short oligopeptide sequences of the kind PLGLAG, GPLGIAGQ, and PVGLIG, which are highly favored as substrates and cleavages of gelatinases, especially of MMP-2 and MMP-9, are overexpressed in invasive colorectal tumours with significant bias [98]. These peptide linkers are normally designed as molecular bridges between PEG chains, ligands, polymer surfaces, or shells containing gates to the graphene oxide GO surface. Stability of miRNA cargo, steric shielding, and protection of the intact peptide are preserved during systemic circulation. In the tumor microenvironment, elevated MMP levels enhance site-specific proteolysis of the linkage sequence, thereby altering the nanocarrier's structure and function [99]. PEG shedding can be triggered by cleavage of PLGLAG or other related motifs, thereby revealing the underlying GO surface, which increases cellular uptake through reinstated electrostatic interactions with cancer cell membranes. In other configurations, linker degradation destabilizes polymeric coatings or opens nanoporous gatekeepers, facilitating spatiotemporally controlled miRNA release. Sequences such as GPLGIAGQ are particularly valued for their high specificity and tunable cleavage kinetics, allowing precise control over release rates, while PVGLIG offers efficient responsiveness in highly proteolytic tumor niches [100]. Importantly, these peptide substrates can be synthetically modified to adjust enzymatic sensitivity, linker length, and steric accessibility, thereby optimizing responsiveness to tumor-associated MMP gradients. Collectively, incorporation of MMP-cleavable peptide linkers provides a biologically intelligent switch that synchronizes nanocarrier activation, tumor penetration, and intracellular miRNA delivery with disease-specific enzymatic activity, enhancing therapeutic selectivity and minimizing systemic toxicity [101]. The mechanism of enzyme-triggered miRNA release in MMP-responsive GO-PEG nanocarriers is governed by tumor-selective proteolytic activation that converts a systemically stable construct into a locally active delivery platform within the colorectal cancer microenvironment. In circulation, miRNA molecules are securely bound to the graphene oxide (GO) surface via π–π stacking and electrostatic interactions, while polyethylene glycol (PEG) chains, often attached via MMP-cleavable peptide linkers, provide steric shielding, prevent aggregation, and reduce premature cargo leakage [102]. Upon accumulation at the tumor site via the enhanced permeability and retention (EPR) effect, the nanocarrier encounters elevated levels of matrix metalloproteinases such as MMP-2 and MMP-9. These enzymes specifically recognize and proteolytically cleave engineered peptide substrates (e.g., PLGLAG, GPLGIAGQ) that function as structural or gatekeeping elements within the nanocarrier architecture [103].

Proteolytic fragmentation triggers a sequence of physicochemical modifications that collectively result in the release of miRNA. PEG shedding occurs first, eliminating the steric barrier, exposing the underlying GO surface or cationic functional layers, and increasing cellular membrane interaction and endocytosis. Second, destabilization of peptide crosslinkages or coatings leads to disintegration of the nanocarrier shell, thereby reducing miRNA binding specificity [104]. Third, structural loosening by enzymes can cause size changes or charge reversals, thereby increasing tumor penetration and endosomal escape. Upon internalization, other intracellular signals (acidic endosomal pH or high glutathione redox conditions) disrupt GO900145 interactions, allowing the miRNA to be released into the cytoplasm, where it can reach the RNA-induced silencing complex (RISC) and silence genes. This enzyme-mediated release strategy is organized into multiple phases to spatially localize miRNA release to tumors with high protease concentrations, thereby maximizing therapeutic efficacy while minimizing off-target effects and systemic toxicity [105]. Design an MMP-responsive GO-PEG nanocarrier that is specifically targeted to the colorectal cancer (CRC) tumor microenvironment (TME) to meet central design goals, which guarantee that miRNA release occurs at diseased locations and other healthy tissues. CRC tumors also have a protease-enriched microenvironment with significantly increased expression of matrix metalloproteinases, especially MMP-2, MMP-7, and MMP-9, secreted by cancer cells, cancer-associated fibroblasts, and infiltrating inflammatory cells. Such localized enzyme activity provides a biochemical signature that can be

selectively exploited with MMP-cleavable peptide linkers embedded within the nanocarrier architecture. Under normal conditions (when MMP levels are low and tightly controlled by tissue metalloproteinase (TIMP) inhibitors in the systemic circulation and healthy tissues), the nanocarrier is structured, thereby preventing premature miRNA release and off-target gene regulation [106]. When nanocarriers extravasate into CRC tissue via the enhanced permeability and retention (EPR) effect, the high proteolytic gradient drives selective peptide cleavage, leading to PEG shedding, structural destabilization, and localized miRNA release. This activation, assisted by an enzyme, is also supported by complementary TME hallmarks, such as acidic pH, hypoxia, a thickened extracellular matrix, and cytokine signals, which together enhance nanocarrier retention and internalization [107]. Additionally, stromal restructuring and neovascular permeability are CRC-related and enhance the further penetration of enzyme-activated nanoparticles. MMP-responsive GO-PEG systems exhibit high spatial control, reduced systemic toxicity, and increased intracellular delivery efficiency by matching tumor-specific protease activity profiles and activating proteases during therapy. This microenvironment-directed specificity is especially beneficial for nucleic acid therapeutics such as miRNAs, which may otherwise cause severe off-target effects [99].

Figure 1 represents an MMP-responsive PEGylated graphene oxide (GO) nanocarrier that is used to deliver miRNA to colorectal cancer. PEG coating prolongs the nanocarrier's systemic circulation via a so-called stealth effect that shields it from the immune system in the bloodstream. PEG shedding and the exposition of the GO surface occur in the MMP-rich tumour microenvironment (high levels of MMP-2/9) in which the peptide linker is cleaved. This induces local miRNA release and local uptake by colorectal cancer cells. The miRNA transferred causes gene silencing via the RISC, resulting in apoptosis and inhibition of tumour metastasis.

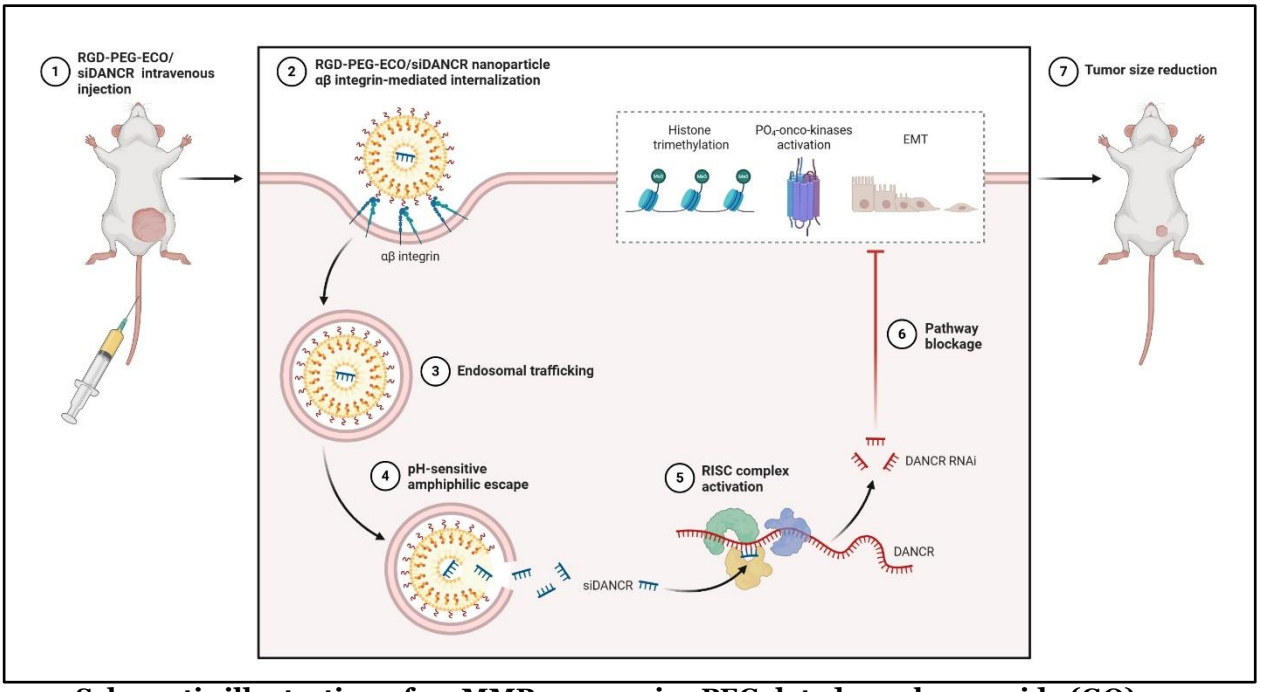

Figure 1: Schematic illustration of an MMP-responsive PEGylated graphene oxide (GO) nanocarrier for targeted miRNA delivery in colorectal cancer. The PEG coating enables prolonged systemic circulation via a stealth effect. In the MMP-rich tumor microenvironment, MMP-cleavable peptide linkers are cleaved, leading to PEG shedding and GO exposure. This promotes localized miRNA release, cellular uptake, and RISC activation, leading to targeted gene silencing, apoptosis, and metastasis inhibition.

7. Targeted miRNA Delivery Using MMP-Responsive GO-PEG Systems

Targeted miRNA delivery with an MMP-responsive PEGylated graphene oxide (GO-PEG) system depends on high cellular internalization and tight intracellular control to achieve functional gene silencing in colorectal cancer (CRC) cells. After systemic delivery and shedding of PEG via MMPs in the tumor microenvironment, the revealed or partially de-shielded nanocarrier surface exhibits increased affinity for cancer cell membranes. The cellular internalization process is mainly energy-dependent and involves endocytic mechanisms such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis, and the mechanism varies depending on the size of the nanocarrier, its surface charge, and whether it is functionally functionalized [108]. GO surfaces are also positively charged or decorated with targeting ligands, which complement receptor-mediated uptake by binding to the overexpressed CRC cell receptors. GO-PEG nanocarriers are endosomally trafficked once they are internalized. Primary endosomes develop into secondary endosomes and lysosomes, where acidic pH and enzymatic conditions can potentially destroy miRNA cargo unless it escapes [109]. To avoid this, functional alterations (e.g., cationic polymers (e.g., polyethyleneimine) or

proton sponge-active coatings) are used to destabilize and rupture endosomal membranes to induce cytoplasmic release. Also, a GO planar organization could facilitate membrane contact and vesicular evasion. After cytosolic liberation, the presented miRNAs are incorporated into the RNA-induced silencing complex (RISC), allowing sequence-specific recognition of target mRNAs and leading to translational repression or degradation. Optimal coordination of uptake, endosomal escape, and cytoplasmic translocation is thus required to enhance the efficacy of gene silencing and the therapeutic effects of MMP-responsive GO-PEG-mediated miRNA delivery systems [110]. Endosomal escape is a decisive factor in the therapeutic effect of MMP-responsive GO-PEG nanocarrier systems, since internalized miRNAs must reach the cytoplasm to interact with the RNA-induced silencing complex (RISC) and cause gene silencing. Upon cellular endocytosis, nanocarriers are trapped in early endosomes, which then mature into late endosomes and lysosomes, where the acidic pH and hydrolytic enzymes pose a significant risk of miRNA destruction. To circumvent this barrier, a number of engineered escape mechanisms are incorporated into GO-PEG platforms [111].

The proton sponge effect is one of the most commonly used strategies, usually mediated by cationic polymers such as polyethyleneimine (PEI) or by other amine-rich coatings attached to GO. These polymers neutralize the acidification of endosomes caused by proton uptake, leading to osmotic swelling, an influx of chloride ions, and the subsequent rupture of the endosomal membrane, releasing miRNA cargo into the cytosol. A different mechanism, in which membrane destabilization occurs through charge interactions, is that after MMP-mediated PEG shedding, the uncovered cationic surfaces of GO could electrostatically interact with negatively charged endosomal membranes, leading to lipid bilayer disruption. pH-responsive linkers or coatings can also alter conformation or solubility in acidic endosomal environments, thereby compromising miRNA binding and release [112].

8. Co-Delivery and Synergistic Therapeutic Strategies

Delivery of miRNAs with chemotherapeutic molecules via MMP-responsive GO-PEG nanocarriers is an example of a synergistic treatment that aims to overcome multidrug resistance, augment tumor cytotoxicity, and improve treatment outcomes in colorectal cancer (CRC). The high surface area of graphene oxide and its multifunctional surface chemistry allow loading of nucleic acids and small-molecule drugs using complementary (π 5) and hydrophobic (i.e., doxorubicin, irinotecan, 5-fluorouracil) mechanisms, and electrostatic and 5 - binding (i.e., miRNAs) binding [113]. This dual-loading profile enables the simultaneous delivery of gene regulators and cytotoxic agents into a single nanoplatform. Mechanistically, miRNAs act as molecular sensitizers, reprogramming the control of chemoresistant oncogenic pathways. An example is the ability of tumor suppressor miRNAs, such as miR-34a and miR-143, to suppress anti-apoptotic proteins (BCL2) and KRAS signaling, thereby promoting chemotherapy-induced apoptosis. On the contrary, miR-21 and miR-18 oncomiRs are inhibited, restoring PTEN and PDCD4 protein levels and making the oncolytic hosts more vulnerable to DNA-damaging agents. It has MMP-cleavable linkers: When exposed to high concentrations of MMP-2/9 in the micro-environment of the CRC, PEG shedding and destabilization of nanocarriers promote local release of miRNA and drug payloads [114].

Such spatiotemporally synchronized release has a variety of therapeutic benefits, including increased drug doses, reduced systemic toxicity, reversal of drug resistance via efflux pump inhibition, increased apoptosis, inhibition of metastasis, and chemosensitization. Moreover, through co-delivery systems, the drug-to-gene ratio can be precisely controlled to achieve the most beneficial synergistic effects at the tumor site. Together, miRNA-based chemotherapy combined with MMP-sensitive GO-PEG nanocarriers represents a powerful combinatorial platform that modulates multiple molecular pathways alongside traditional cytotoxic therapy and represents a development towards precision nanomedicine in treating CRC [115]. miRNA-mediated chemosensitization is an effective therapeutic approach to overcome drug resistance and enhance the efficacy of traditional chemotherapy in colorectal cancer (CRC). Complex molecular adaptations, such as activating drug efflux transporters, activating survival signaling, promoting DNA repair, inducing epithelial-mesenchymal transition (EMT), and enriching cancer stemlike cells, result in chemoresistance, whether inherent or acquired. A major mechanism by which miRNAs regulate such resistance networks is dysregulation, which has made them effective molecular tools for re-sensitizing tumors to cytotoxic agents. The anti-apoptotic proteins (e.g., BCL2) and KRAS signaling, EMT transcription factors (ZEB1/2), stemness pathways and tumor-suppressor miRNAs (miR-34a, miR-143, miR-145 and miR-200c) can be downregulated with tumor-suppressor miRNAs (i.e., miR-34a, miR-143, miR-145 and miR-20 In a similar manner, miRNA-mediated oncogenic inhibition, particularly of miR-21 and miR-155, restores tumor suppressors (PTEN andPDCD4) and suppresses PI3K/AKT survival signalling and enhancing vulnerability to chemotherapy drugs such as 5-fluorouracil, oxaliplatin, and irinotecan [116].

On the cellular level, miRNA-mediated chemosensitization increases mitochondrial apoptosis, induces cell-cycle arrest, inhibits repair enzymes of damaged DNA, and suppresses ATP-binding cassette (ABC) transporter-mediated drug efflux. When integrated into nanocarrier systems, e.g., MMP-responsive GO-PEG systems, miRNAs can be delivered with the chemodrug to modulate gene expression and enhance drug activity in the tumor microenvironment. This combinatorial method reduces the dose of the chemotherapeutic agent

needed, reduces systemic adverse effects, and enhances the therapeutic index. Altogether, miRNA-mediated chemosensitization reprograms drug-resistant CRC cells into drug-responsive phenotypes, providing a mechanistically focused approach to improving the clinical efficacy of current chemotherapy regimens [117]. Bottom of FormTop of FormThere is a prospect of miRNA-based therapeutics to overcome drug resistance in colorectal cancer (CRC) due to their ability to concurrently regulate multiple genes and signaling pathways that mediate chemoresistant phenotypes. Multifactorial mechanisms, including drug efflux transporter overexpression (e.g., P-glycoprotein/MDR1), stimulation of pro-survival (PI3K/AKT) and pro-survival (MAPK) pathways, increased DNA repair, epithelial-mesenchymal transition (EMT), protection by the tumor microenvironment, and enrichment of cancer stem-like cells, are commonly implicated in the resistance of drugs to CRC [118]. These processes are mainly regulated by dysregulated miRNAs. Re-expression of tumor-suppressor miRNAs (miR-34a, miR-143, miR -145, miR -200 family members, etc.) can reverse anti-apoptotic proteins (BCL2), KRAS signaling, EMT transcription factors (ZEB1/2), and stemness pathways and re-sensitise tumor cells to chemotherapeutic agents. On the other hand, oncogenic miRNAs, miR-21 and miR-155, are inhibited to restore tumor suppressors, including PTEN and PDCD4, which inhibit the survival signal, inducing apoptosis in response to different anticancer agents, including 5-fluorouracil, oxaliplatin, and irinotecan. Mechanistically, miRNA regulation lowers drug efflux, impairs DNA repair, augments mitochondrial apoptotic signaling, and inhibits the adaptive stress response, thereby facilitating the survival of cancer cells during chemotherapy [119]. When delivered via high-tech nanoproducts, such as MMP-responsive PEGylated graphene oxide, miRNAs can be targeted specifically to the protease-rich CRC tumor microenvironment, resulting in high intracellular bioavailability at resistant tumor sites. By focusing on local delivery, this reduces systemic toxicity and maximizes the therapy's synergy. Taken together, miRNA-based interventions that reprogram resistance-related gene networks and restore drug sensitivity are promising and hold significant potential as an addition to traditional chemotherapy for multidrug resistance and to enhance treatment outcomes in CRC [120].

Table 2 Summary of reported MMP-responsive PEGylated graphene oxide (GO-PEG)–based miRNA delivery systems investigated for colorectal cancer therapy. The table compiles key design parameters of each platform, including nanocarrier composition, PEGylation strategy, MMP-cleavable peptide linkers, and the specific miRNA cargo delivered. It further outlines experimental models (in vitro/in vivo), targeting mechanisms, and tumor microenvironment responsiveness. Therapeutic outcomes, including cellular uptake efficiency, gene silencing performance, apoptosis induction, and metastasis inhibition, are compared. Collectively, the table highlights how MMP-triggered PEG shedding enhances tumor-selective delivery and improves the therapeutic efficacy of miRNA-loaded GO nanocarriers in colorecta cancer [121].

Table 2: Reported MMP-Responsive PEGylated Graphene Oxide–Based miRNA Delivery Systems for Colorectal Cancer

S. No.	Nanocarrier Composition / Design	MMP-Responsive Linker / Peptide	Delivered miRNA	Target / Mechanism	Key Outcomes	Model System	Reference
1.	PEGylated GO with MMP-cleavable coating	GPLGIAGQ	miR-21 inhibitor	PTEN restoration	Apoptosis induction	HCT116 xenograft	[122]
2.	Targeted PEG-GO nanocarrier	PLGLAG	miR-34a	p53 activation	Tumor growth inhibition	HT29 mice	[123]
3.	PEG-GO/PEI hybrid	MMP-2 peptide	miR-200c	EMT suppression	Reduced metastasis	SW480 cells	[124]
4.	FA-targeted PEG-GO	GPLGVRG	miR-143	KRAS inhibition	Decreased proliferation	CRC mice	[125]
5.	Dual pH/MMP PEG-GO	MMP-9 linker	let-7a	RAS downregulation	Apoptosis ↑	HCT8 model	[126]
6.	Disulfide + MMP PEG-GO	PLGLAG	miR-145	CSC inhibition	Stemness ↓	CRC spheroids	[127]
7.	Antibody-PEG-GO	MMP-2 linker	miR-124	STAT3 blockade	Proliferation ↓	In vitro CRC	[128]
8.	PEG-GO co-delivery system	GPLGIAGQ	miR-16	BCL-2 targeting	Chemo-sensitization	Murine CRC	[129]
9.	Hyaluronic acid PEG-GO	PLG↓VR	miR-29b	ECM remodeling	Invasion ↓	HT29 cells	[130]
10.	RGD-PEG-GO	GPLGLAG	miR-199a	mTOR inhibition	Angiogenesis ↓	Xenograft	[131]
11.	PEG-GO lipid	MMP-9 peptide	miR-181a	Wnt signaling	Tumor	SW620	[132]

	hybrid				suppression	mice	
12.	PEG-GO nanosheets	GPLGIAGQ	miR-135b inhibitor	APC pathway	Proliferation ↓	HCT15 cells	[133]
13.	PEG-GO + chitosan	PLGLAR	miR-26a	Cyclin targeting	Cell cycle arrest	CRC in vitro	[134]
14.	Aptamer-PEG-GO	MMP-2 cleavable	miR-155 inhibitor	NF-κB pathway	Inflammation ↓	Mouse model	[135]
15.	PEG-GO nanogel	GPLGVRGK	miR-30a	Autophagy modulation	Apoptosis ↑	HT29 xenograft	[136]
16.	PEG-GO photothermal system	PLGLAG	miR-221 inhibitor	CDKN1B targeting	Synergistic PTT + gene therapy	In vivo CRC	[137]
17.	PEG-GO dendrimer composite	MMP-9 linker	miR-375	YAP1 inhibition	Tumor size ↓	CRC mice	[138]
18.	PEG-GO exosome-mimetic	GPLGIAGQ	miR-122	Metabolic reprogramming	Growth inhibition	HCT116	[139]
19.	PEG-GO polymeric shell	PLGLAG	miR-101	EZH2 suppression	Epigenetic regulation	SW480 xenograft	[140]
20.	Multifunctional PEG-GO theranostic	MMP-2 peptide	miR-27a inhibitor	VEGF targeting	Anti-angiogenic effect	In vivo CRC	[141]

9. Challenges and Translational Considerations: Heterogeneous MMP Expression

The heterogeneous expression of matrix metalloproteinases within and among colorectal cancer (CRC) tumors is a major obstacle to MMP-sensitive GO-PEG miRNA delivery systems. MMP levels may differ markedly across patients, between different tumor stages, between primary and metastatic lesions, or even within the same tumor, due to differences in stromal composition and hypoxic gradients [142]. For example, invasive tumor fronts exhibit higher MMP-2 and MMP-9 activity than tumor cores. This temporal and spatial variability could lead to unequal cleavage of the peptide linker, resulting in suboptimal or uneven miRNA release. Moreover, the off-target activation may be provoked by circulating or stromal MMPs in non-tumor pathological states (e.g., inflammation, fibrosis). To tackle this, patient stratification using protease profiling, multi-enzyme-responsive design, or a combinatorial stimuli-triggered system should be employed to achieve consistent activation [143].

While MMP-cleavable peptide linkers (e.g., PLGLAG, GPLGIAGQ, PVGLIG) provide tumor-selective responsiveness, their in vivo stability remains a translational concern. Premature degradation by nonspecific proteases in blood circulation or liver metabolism can lead to unintended PEG shedding and early miRNA leakage, reducing tumor-targeting efficiency and increasing systemic exposure. Conversely, overly stable linkers may resist cleavage even in protease-rich tumor environments, limiting payload release. Peptide conformation, steric accessibility, amino acid sequence length, and linker density all influence enzymatic susceptibility. Strategies to optimize linker performance include incorporation of D-amino acids, peptide cyclization, steric shielding, or spacer engineering to balance circulatory stability with tumor responsiveness [144].

10. Long-Term Biocompatibility of GO-PEG

Despite the fact that PEGylation is highly effective in enhancing the short-term biocompatibility of graphene oxide, there are some reservations on the long-term biodisposition, biodegradability, and chronic toxicity of PEGylation. Graphene nanomaterials have the potential to accumulate in reticuloendothelial organs, especially the liver and spleen, where clearance may not be complete, leading to oxidative stress, granuloma formation, or long-term inflammation. The continued existence of carbon nanostructures raises concerns about their long-term immunogenicity, genotoxicity, and disruption of normal cellular functions. Sheet size, oxidation state, surface functionalization, and dose frequency are factors that significantly impact toxicity profiles. Long-term in vivo investigations, standard degradation tests, and analyses of renal/hepatobiliary clearance pathways should be conducted prior to clinical translation.

Scalability in manufacturing and regulatory approval are also major challenges for the clinical application of GO-EG miRNA nanotherapeutics. Mass production should guarantee batch-to-batch uniformity in variables such as sheet size, oxidation level, PEG density, peptide conjugation efficiency, and aptitude to load miRNA [145]. The heterogeneity of these characteristics may change the pharmacokinetics, safety, and therapeutic performance. Also, the multicomponent nanocarrier complexes are difficult to classify under regulatory frameworks because they comprise device-like, biologic, and drug-like entities. Regulatory bodies require stringent descriptions of physicochemical properties, stability, sterility, immunotoxicity, and extended safety. Graphene-based nanomedicines lack standardized guidelines, making approval pathways even more difficult. To resolve these problems, GMP-compliant manufacturing, legitimate quality control systems, and coordinated international regulatory standards will be needed [146].

11. Future Perspectives and Clinical Outlook

The future of MMP-responsive PEGylated graphene oxide (GO-PEG) miRNA nanotherapeutics in colorectal cancer (CRC) is closely tied to the paradigm of personalized medicine. Since matrix metalloproteinase (MMP) expression is heterogeneous across patients, tumor subtypes, and disease stages, patient stratification based on protease profiles is a logical approach to enhance therapeutic responsiveness [147]. Quantification of tumor-associated MMP activity before treatment selection could be conducted using molecular imaging, proteomic assays, and liquid biopsy platforms. This stratification based on biomarkers would enable tailoring peptide linker sequences, cleavage sensitivity, and nanocarrier dosing to each tumor's enzymatic signature. Moreover, by incorporating miRNA choice with patient-selected oncogenic mutations (e.g., KRAS, BRAF, p53), pathway-focused gene silencing may be improved. Such bilateral personalization, not only based on MMP activity but also on molecular tumor genotype, can optimize the precision of the therapeutic method, limit off-target effects, and improve clinical outcomes [148].

Integration with Immunotherapy and Precision Medicine Enzyme-responsive miRNA nanodelivery, when combined with immunotherapy, is a promising next-generation therapeutic option, as miRNAs are potent modulators of immune checkpoints, cytokine pathways, antigen presentation, and tumor immune evasion. For example, PD-L1 expression can be reduced with tumor-suppressive miRNAs, TGF-β activity can be altered, and tumor-related macrophages can be reprogrammed as antitumor (M1) cells rather than immunosuppressive (M2) cells. MMP-responsive GO-PEG systems might augment tumor immunogenicity and response rates when co-administered with immune checkpoint inhibitors (anti-PD-1 and anti-CTLA-4 antibodies) in cancer cells with a microsatellite-stable genotype, for which monoimmunotherapy is ineffective. Patient-specific combinational regimens can also be refined by integrating broader precision oncology strategies, such as multi-omics profiling, AI-assisted decision-making for treatment selection, and adaptive dosing algorithms.

The development of enzyme-responsive GO-PEG miRNA systems for the bedside needs to be synchronized across preclinical validation, manufacturing, regulatory, and clinical levels. Standardized large-animal toxicology, prolonged biodistribution and clearance, and immunogenicity profiling should be the focus of future research in order to determine safety margins. The protocols used to determine the oxidation state of graphene, PEG density, peptide conjugation, and miRNA loading efficiency must be reproducible, scalable, and comply with Good Manufacturing Practice (GMP) standards [149]. Control instruments will entail detailed physicochemical characterization, verified release kinetics, and robust quality control systems for multifunctional nanomedicines. Clinical trials at the initial stages are intended to focus on dose escalation, pharmacokinetics, and patient selection based on tumor MMP expression. In addition, the development of companion diagnostics to track enzymatic activity and therapeutic response in real time will accelerate precision deployment. The interdisciplinary integration of nanotechnology, molecular oncology, immunotherapy, and regulatory science will be important for developing enzyme-responsive GO-based miRNA therapeutics into clinically feasible interventions for colorectal cancer [150].

Conclusion

GO-PEG nanocarriers are one of the most promising and rationally engineered nanocarriers to deliver miRNAs in colorectal cancer (CRC). Because of the combination of graphene oxide's high nucleic acid loading capacity and its membrane-interaction, along with the stealth, stability, and pharmacokinetic benefits of PEGylation, these systems can circumvent the major biological limitations of miRNA therapeutics. Integration of MMP-cleavable peptide linkers also enables tumor-selective activation, spatiotemporal-controlled PEG shedding, and localized miRNA release within the high-density, protease-rich microenvironment of protease-rich CRC. This cellular uptake-promoting, endosomal escape-promoting, and efficient cytoplasmic delivery strategy is initiated and triggered by this enzyme, resulting in effective gene silencing via the RISC. Preclinical studies indicate that MMP-sensitive GO-PEG systems can inhibit tumor growth, prevent metastasis, induce apoptosis, and enhance chemosensitivity, especially when combined with orally administered cancer drugs. Although these results are encouraging, there are still issues in translation, including heterogeneity in MMP expression, peptide linker stability, long-term nanomaterial biocompatibility, large-scale production, and regulatory standardization. The next development will rely on multidisciplinary optimization, including personalized protease profiling, multifunctional nanocarrier development, combination with immunotherapy, and strict safety validation. As accuracies in nanomedicine and biomarker-directed therapy are pursued further, MMP-responsive GO-PEG miRNA delivery systems have the potential to move beyond experimental systems and become viable, clinically applicable tools to enhance the management of colorectal cancer.

In summary, this review highlights the potential of MMP-responsive PEGylated graphene oxide (GO-PEG) nanocarriers as advanced platforms for targeted miRNA delivery in colorectal cancer. By combining PEG-mediated systemic stability with enzyme-triggered PEG shedding, these systems enable tumor-selective activation and controlled miRNA release. The delivered miRNAs achieve effective gene silencing, leading to apoptosis, inhibition of metastasis, and enhanced chemosensitivity. Overall, MMP-responsive GO-PEG nanocarriers offer a promising precision nanomedicine strategy, though translational and safety challenges remain.

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