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Nanoparticle-mediated delivery of microRNAs-based therapies for treatment of disorders

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ABSTRACTS

miRNAs represent appropriate candidates for treatment of several disorders. However, safe and efficient delivery of these small-sized transcripts has been challenging. Nanoparticle-based delivery of miRNAs has been used for treatment of a variety of disorders, particularly cancers as well as ischemic stroke and pulmonary fibrosis. The wide range application of this type of therapy is based on the important roles of miRNAs in the regulation of cell behavior in physiological and pathological conditions. Besides, the ability of miRNAs to inhibit or increase expression of several genes gives them the superiority over mRNA or siRNA-based therapies. Preparation of nanoparticles for miRNA delivery is mainly achieved through using protocols originally developed for drugs or other types of biomolecules. In brief, nanoparticle-based delivery of miRNAs is regarded as a solution for overcoming all challenges in the therapeutic application of miRNAs. Herein, we provide an overview of studies which used nanoparticles as delivery systems for facilitation of miRNAs entry into target cells for the therapeutic purposes. However, our knowledge about miRNA-loaded nanoparticles is limited, and it is expected that numerous therapeutic possibilities will be revealed for miRNA-loaded nanoparticles in future.

1. Introduction

MicroRNAs (miRNAs) are small transcripts with sizes about 22 nucleotides that regulate gene expression mainly through induction of mRNA degradation [35]. They are involved in the regulation of important cellular activities, including metabolic pathways [68], differentiation and proliferation of cells [12] and apoptosis [25]. These small-sized transcript affect the evolution and progression of diseases, including cancer [14,17], neurodegenerative diseases [44], cardiovascular disorders [15], and other conditions [16,24]. Based on their important functions in diverse processes, they are considered as candidates for treatment of human disorders. Therefore, several efforts have been done to facilitate their entry into specific cells. The capacity of nanoparticles (NPs) to protect the loaded agent from the external environment, thereby decreasing inactivation or degradation, increasing circulation time, and facilitating targeted accumulation, has led to their suggestion as a delivery vehicle for miRNA [43,56]. Nanoparticles are very small particles, typically between 1 and 100 nm in size. A variety of categories can be created for NPs according to their characteristics, shapes, and dimensions. The physical and chemical properties of NPs are unique because of their nanoscale size and large surface area, which make them suitable for delivering miRNAs into specific cells (Fig. 1).

In this regard, nanoparticle carriers have offered extraordinary chances for regulated cell specific delivery of miRNAs as therapeutic modalities [28]. This type of delivery system can overcome the

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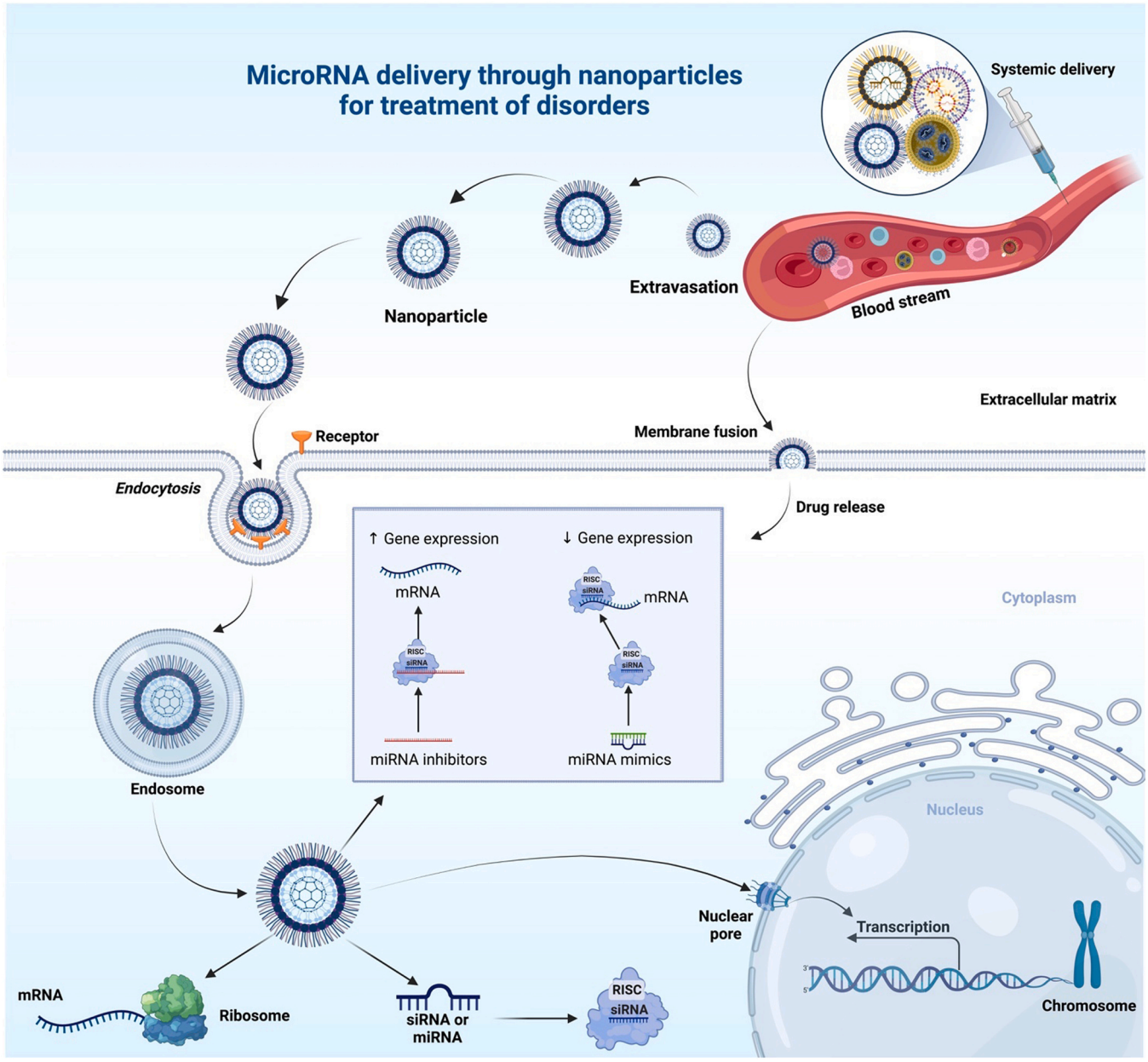

Fig. 1. miRNA-loaded nanomedicine-based approach. MiRNAs can either repress or activate genes involved in cancer, depending on their target. Obtained from https://app.biorender.com/biorender-templates.

limitation of miRNAs efficacy in treatment of disorders through enhancing their targeting ability, increasing circulation time and decreasing off-target effects which are associated with naked miRNA-based agents [28]. In fact, nanoparticles are able to protect the loaded agent from the external environment, thus decreasing inactivation or degradation, and increasing circulation time and accumulation of the agent in the target tissues [1]. Another point to be emphasized is that the ability of miRNAs to instantaneously regulate several mRNAs gives them the superiority over other therapeutic agents. Moreover, miRNAs can be used in the form of miRNA inhibitors and miRNA mimics, and they have a small size that simplifies their encapsulation into nanoparticles and their delivery into target cells [28].

Herein, we provide an overview of studies which used nanoparticles as delivery systems for facilitation of miRNAs entry into target cells for the therapeutic purposes. This information is classified based on the type of disorders in which this strategy has been used.

2. Nanoparticle-mediated delivery of miRNAs for treatment of gastrointestinal disorders

Nanoparticle-based delivery of miRNAs can be used as a treatment modality for hepatoma since it can combat the inherent chemoresistance of hepatoma. Xiong et al. have constructed a cyclodextrin-cored star copolymer nanoparticle system to co-deliver miR-122 with doxorubicin for treatment of hepatoma. This system allows a chronological release of miR-122 and doxorubicin (Fig. 2). miR-122 can induce cell apoptosis through decreasing Bcl-w and enhancing p53 activity. Moreover, it can increase accumulation of doxorubicin via suppression of cytotoxic efflux transporter expression. The efficacy of this delivery system has been confirmed in animal models [57].

Expression of miR-17 family has been found to be increased in a number of hepatocellular carcinoma (HCC) tumors and cell lines. Huang et al. have established a miR-17 family target gene profile. Then, a lipid nanoparticle encapsulating a potent anti-miR-17 family oligonucleotide,

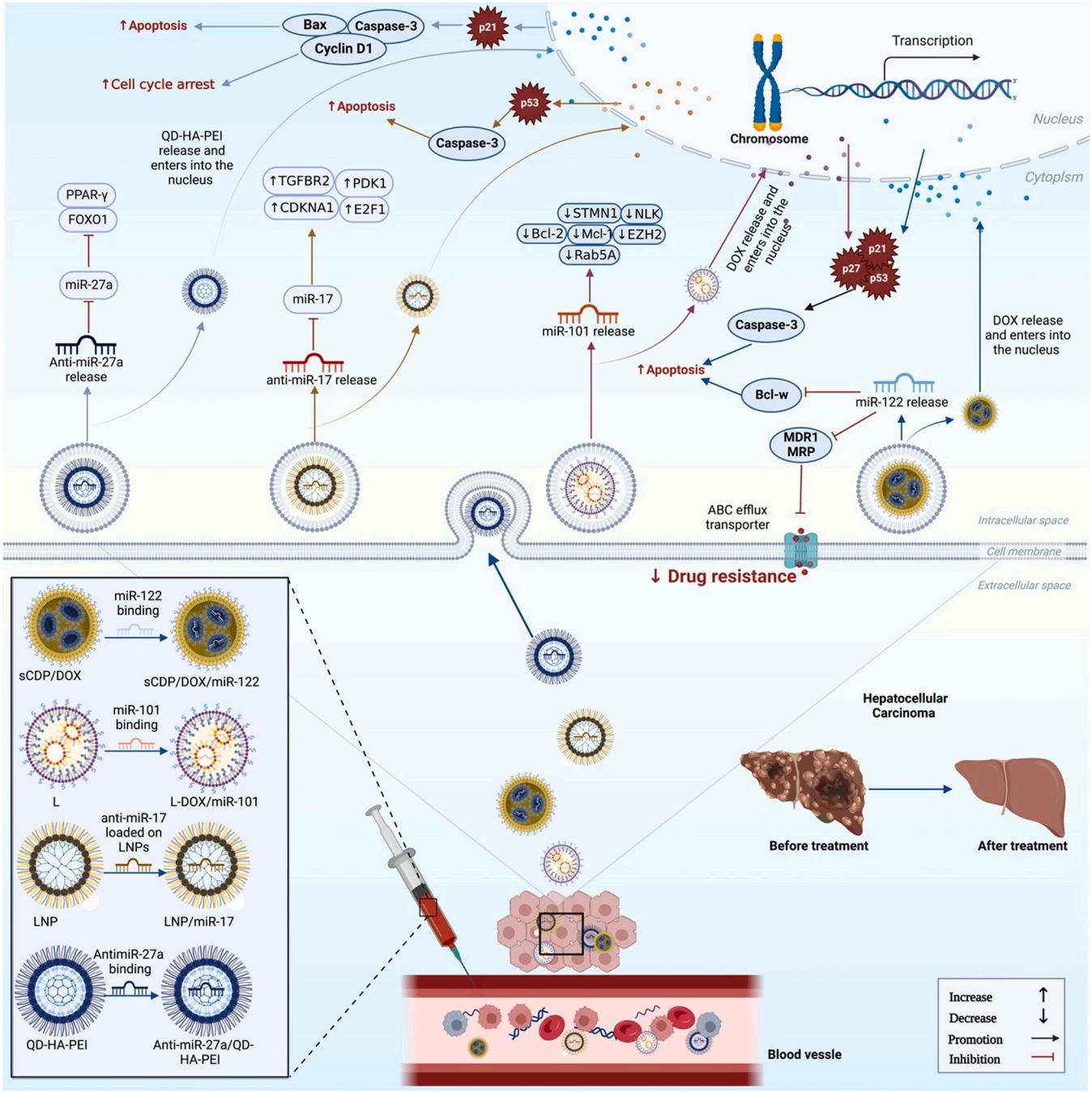

Fig. 2. Schematic depiction of nanoparticle-based miRNA therapy for hepatocellular carcinoma. After being taken up by hepatoma cells, miRNA-based nanoparticles escape from the lysosome. Afterward, miRNAs are entered into the cytoplasm, and DOX is released into the nucleus. Both released miRNAs and DOX inhibit the tumor related malignant characteristics of HCC cells by acting on their respective target genes, resulting in simultaneous anticancer actions in HCC.

namely RL01–17(5), was used for suppression of expression of this miRNA family. Systemic administration of RL01–17(5) to orthotopic xenograft model of HCC has led to inhibition of tumor growth in correlation with over-expression of miR-17 family targets [23]. In another study, Xu et al. have prepared liposome (L) nanoparticles for simultaneous delivery of miR-101 and doxorubicin to HCC cells. The efficiency of this delivery system has been approved in subcutaneous xenograft models of HCC cells. miR-101/doxorubicin-L could inhibit malignant properties of HCC via targeting correlative genes [58]. Nanoparticle-based delivery of miRNAs has also been used for treatment of pancreatic, gastric and colorectal cancers as well as liver ischemia reperfusion (I/R) injury. Table 1 summarizes the nanoparticle-mediated delivery of miRNAs for treatment of gastrointestinal disorders.

3. Nanoparticle-mediated delivery of miRNAs for treatment of breast cancer

Nanoparticle-based delivery of miRNAs has been used for treatment of breast cancer. For instance, to get miR-34a into triple-negative breast cancer cells and tissues, researchers have employed hyaluronic acid/protamine sulfate nanocapsules. The targeting of CD44 and Notch-1-signaling pathways by miR-34a caused apoptosis and cell death in

Table 1
Nanoparticle-mediated delivery of miRNAs for treatment of gastrointestinal disorders.

Diseases	miRNA	Nanoparticles	Model	Cell lines	Targets	Observation	Ref.
Hepatoma	miR-122	cyclodextrin-cored star copolymer nanoparticle (sCDP); miR-122/DOX/sCDP	xenograft mouse model; [miR-122 (50 nmol/kg) and DOX (2.0 mg/kg)]	HepG2; treated with sCDP (10.0 μg/mL), DOX (2 μg/mL), and miR-122 (50 nM), for 48 h	Bcl-w, p53, MDR1, MRP, Caspase-3	sCDP/DOX/miR-122 could increase efficacy of chemotherapy via inhibiting cytotoxic efflux and inducing apoptosis.	[57]
Hepatocellular Carcinoma (HCC)	miR-17	lipid nanoparticles (LNPs, RL01); anti-miR-17 loaded on RL01	male SCID/Beige mice; treated with anti-miR-17-RL01 (0–2 mg/kg, 3 times/ week)	SK-HEP-1, THLE-2, Hep3B, SNU-398, HuH-7, SNU-475, PLC/PRF/5; treated with anti-miR-17 (1–10 nmol/L)	TGFBR2, CDKN1A, E2F1, BTG3	Inhibition of miR-17 could induce Suppression of HCC growth.	[23]
HCC	miR-17	Lipid nanoparticle (LNP); anti-miR-17 loaded on LNPs	LAP-tTA and TetO-MYC mice, treated with anti–miR-17 (25 nM)	Mouse MYC-driven HCC cells; treated with LNPs-anti-miR-17 (25 nM), for 24 h	E2f1, Tgfbr2, Cdkna1	In MYC-driven HCC, tumorigenesis could be decreased by anti-miR-17.	[10]
HCC	miR-101	liposome (L) nanoparticles	BALB/c athymic nude mice	Huh7, HepG2, SMMC-7721, treated with miR-101/DOX-L (miR-101, 100 nmol/ L), (DOX, 1 μg/mL)	Mcl-1, Rab5A, STMN1, Bcl-2, Caspase-3, EZH2, NLK,	MiR-101/DOX-L could inhibit tumorigenesis and induce apoptosis.	[58]
HCC	miR-221	Poly (lactic-co-glycolic) acid (PLGA)-based nanoparticle, nanoparticle/miR-221 inhibitor	Human, male BALB/c nude mice, treated with miR-221/ nanoparticle (1 nmol), tail vein injection, twice/5 days, for less than 1 month	Bel-7402, HepG2, Huh7, HCCLM3, LO-2; treated with miRNA (10 μL) per well, for 48 h	-	The complex of nanoparticle/miR-221 inhibitor could influence HCC cells by suppressing tumorigenesis.	[30]
Liver Cancer	miR-27a	QD- hyaluronic acid-polyethyleneimineconjugate (HA-PEI) nanoparticle; anti-miR-27a-loaded QD-HA-PEI	male nude mice, treated with QD-HA-PEI-anti-miR-27a (20 nmol/kg, I.V)	HepG2, HL-7702, NIH-3T3, treated with QD-HA-PEI-anti-miR-27a (200 nM), for 24 h	FOXO1, PPAR-γ, Caspase-3,	Anti-miR-27a/QD-HA-PEI could balance the expressions of FOXO-1 and PPAR-γ that showed anti-cancer effects.	[64]
Pancreatic Ductal Adenocarcinoma (PDAC)	miR-212	Chimeric peptide (PL-1), miR-212 loaded on PL-1	Human, male nude mice; DOX (2 mg/kg, I.P,) and nanoparticles (10 μgmiR-212, I.V, every 2 days, for 14 days)	CFPAC-1, A549, PAN-198, CAPAN-1, NCI-H1299, HPNE, Huh7; treated with PL-1/ Cy3-miR-212 (50 nM), for 6 h	USP9X, Vimentin, LC-3I/II, Caspase-3	The complex of miR-212/PL-1 could elevate PDAC cell death via decreasing USP9X.	[6]
Pancreatic Cancer (PC)	exmiR-21, exmiR-10b	Tethered cationic lipoplex nanoparticle (TCLN)	Human, female BALB/C nude mice	-	-	TCLN biochip could determine exmiR-21 levels to diagnose early-stage PC.	[40]
PC	miR-634	lipid nanoparticles (LNPs); miR-634 loaded on LNPs	female BALB/c nude mice; treated with LNPs-miR-634 (5 mg/ kg), I.V, day 7, 9, 12, and 14	PANC-1, CAPAN-1, CAPAN-2, Mpanc96, Hs766T, CFPAC-1, MIAPaCa-2, PH61N; treated with LNPs-miR-634 (20 nmol/L)	OPA1, TFAM, APIP, XIAP, BIRC5, NRF2, LAMP2, caspase-3, PARP	miR-634 loaded on LNPs could decrease tumor growth as a promising therapy.	[18]
Gastrointestinal Stromal Tumors (GIST)	miR-218	O-carboxymethylchitosan (OCMC)-tocopherol (TCP) polymer, miR-218 loaded polymeric nanoparticle	-	293 T, GIST882; treated with miR-218-NPs (100 nM), 48 h	KIT1	The loaded TCP with miR-218 by blocking the cell cycle could induce cell death.	[50]
Colorectal Cancer (CRC)	miR-1321	Zinc oxide nanoparticles (ZONs)	BALB/c nude mice; treated with ZONs (2 mg/kg, S.Q)	HCT116 and HCT8/ Oxa (0.1–10 μm), HCT116, HCT8, treated with ZONs	HIF-2α, ABCG2, Nanog, Bmi1, c-Myc, Sox2,	ZONs via the miR-1321 and HIF-2α could decrease chemotherapy resistance in CRC cells.	[61]
CRC	miR-139–5p	EpCAM aptamer-functionalized cationic liposome-based nanoparticles; miR-139–5p-EpCAM Apt-HSPC/DOTAP/ Chol/DSPE-PEG2000-COOH nanoparticles, MANPs)	male and female BALB/c nude mice; treated with MANPs [miR mimics (1.5 mg/kg)], 7 injections	HCT8, HCT116, SGC7901, HeLa, HCT116-luc, treated with MANPs (100 nmol/L)	MMP2, Bcl-2, E/N-Cadherin, NOTCH1,	MANPs could transmit miR-139–5p into CRC cells and therefore could be a reliable treatment for CRC.	[63]

(*continued on next page*)

Table 1 (*continued*)

Diseases	miRNA	Nanoparticles	Model	Cell lines	Targets	Observation	Ref.
Colon Tumor	miR-224	NMOF-CS-FA-LNA-antisense miR-224 (MCFL224)	-	HCT116, CRL1831; treated with 125 nM of MCFL224 nano-complex	BECLIN1, mTORC1, Caspase-9	MCFL224 as a nanocomposite could be used in the treatment of colon cancer.	[38]
Gastric Cancer	miR-21	anti-miR21 and RSV (resveratrol)-loaded HA (hyaluronic acid)/MSN (mesoporous silica nanoparticles)	SD rats, Balb/c-nu/nu mice; RSV (10 mg/kg) and anti-miR21 (0.45 mg/kg)	BGC823, SGC-7901; treated with HA/RSVmirNP-coumarin-6 (2.5 μg/mL), for 2 h	-	HA/RSVmirNP could be considered a new drug delivery system for GC therapy.	[22]
Liver Ischemia Reperfusion (I/R) Injury	miR-449b-5p	spermidine-PLGA nanoparticles, miR-449b-5p loaded on spermidine/PLGA	Male SD rats; treated with PN-miR mimic (80 mg/kg, tail vein injection)	LO2; treated with PN-miR mimic (0.1–100 μg/mL)	HMGB1, TNFα, IFN-ϒ, IL-1, NF-kB, p-p65,	miR-449b-5p could prevent infection and decrease apoptosis via inhibiting HMGB1 and NF-kB and p-p65 pathways.	[21]

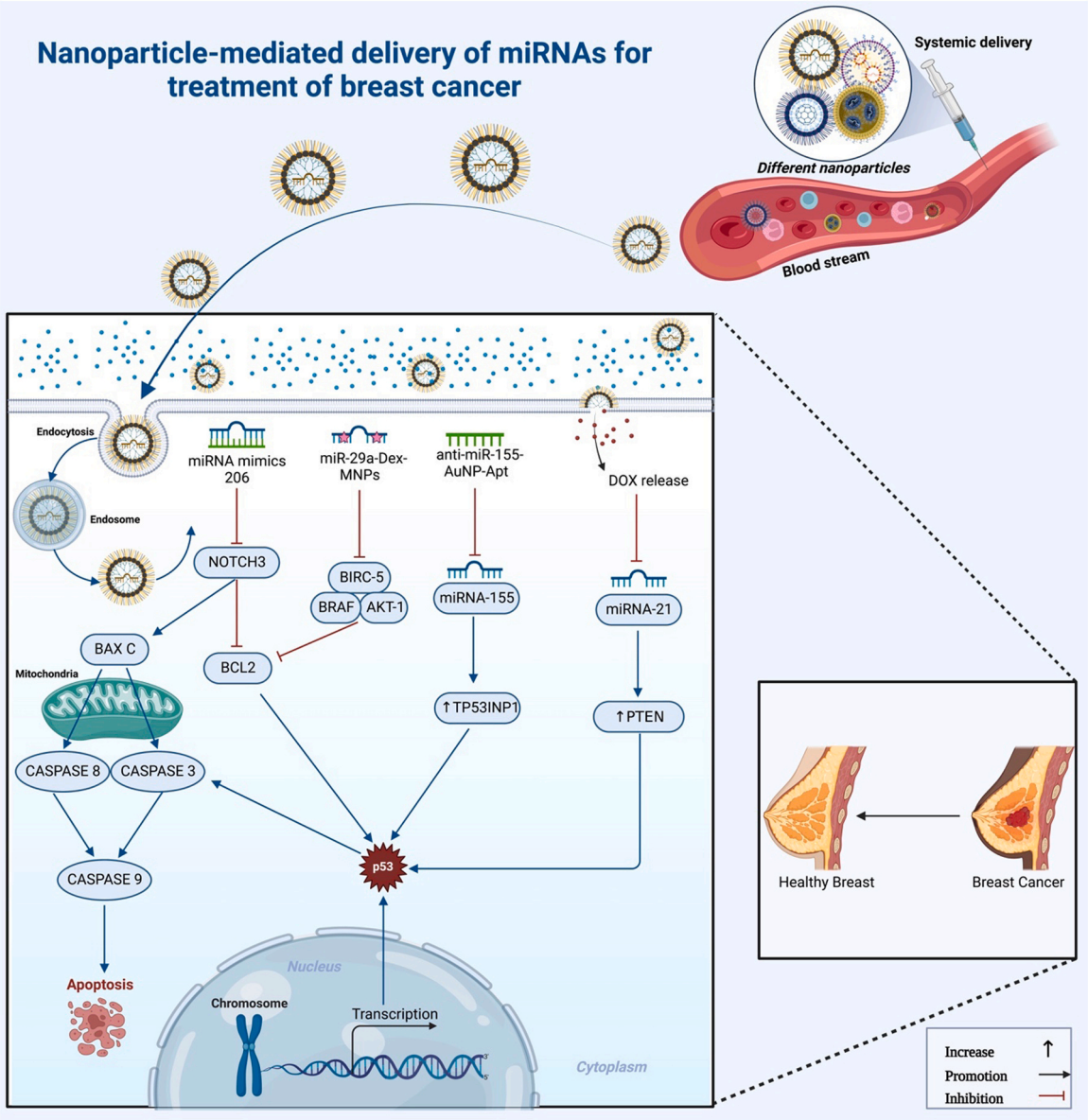

Fig. 3. Targeting breast cancer cells with nanoparticle-mediated delivery of miRNAs.

breast cancer cells, as well as a decrease in migration and proliferation [53]. Similarly, chitosan nanoparticles loaded with doxorubicin and miR-34a were delivered into breast cancer cells to enhance the drug's therapeutic value [9]. Another study has shown that Chitosan nanoparticle up-regulates expression of miR-34a to decrease proliferation, migration and invasion of MDA-MB-231 cells [60]. Furthermore,

Table 2
Nanoparticle-mediated delivery of miRNAs for treatment of breast cancer.

Disease	miRNA	Nanoparticles	Model	Cell lines	Targets	Observation	Ref.
Breast cancer (BCa)	miR-155	Gold nanoparticles (GNPs), AuNP–Apt (AS1411 aptamer)–anti-miR-155	-	MCF-7, CHO-K1; treated with AuNP–Apt (0.05 mM) + anti-miR-155 (15 nM), for 24 hr	TP53INP1	anti-miR-155-AuNP-Apt could be used as a potential therapeutic way via targeting TP53INP1.	[26]
BCa	miR-34a	Chitosan (CS), CS/miR-34a nanoparticles (NPs)	-	MDA-MB-231, HUVECs; treated with miR-34a-CS (100 μL), for 24–48 hr	-	CS/miR-34a NPs could suppress BCa cell growth.	[60]
BCa	miR-29a	Dex (Dextran)-MNPs (iron oxide nanoparticles)/miR-29a	-	MCF-7; treated with Dex-MNPs/miR-29a (0.5–30 nM)	AKT-1, Bcl-2, BIRC-5,	Dex-MNPs/miR-29a could change the expression of apoptotic genes.	[59]
BCa	miR-206	Gold nanoparticles (AuNPs); miR-206 mimic loaded on PEG-AuNPs	-	MCF-7, treated with miR-206-PEG-AuNPs (0.1–5 nM), for 24 h	NOTCH3, Bax, Bcl-2, Caspase-8/9	miR-206-AuNPs could decrease tumorigenesis.	[4]
BCa	miR-21	Calcium phosphate-polymeric nanoparticles (CaP-NPs); miR-21i loaded on CaP-NPs	-	MDA-MB-231, A549; treated with CaP-NPs-miR-21i (10 nM), for 48 h	PTEN, TIMP3, PDCD4,	CaP-coated lipid/PLLA NP could improve the cytotoxic efficacy of doxorubicin by suppressing miR-21 and inducing PTEN.	[47]
BCa	miR-34a	VISA nanoparticle; TV-miR-34a	Human, BALB/c-nude mice, treated with T-VISA-miR-34a (100 μL)	MDA-MB-231, BCSC, XM322, XM607; treated with TV-miR-34a (1 μg)	C22ORF28, TNF-α	T-VISA-miR-34a could inhibit tumor-initiating properties by targeting C22ORF28.	[31]
Triple-Negative Breast Cancer (TNBC)	miR-708	gold nanoparticle (AuNPs), miR-708 loaded on AuNPs	CB-17 SCID mice, CB17. CgPrkdc^{scid}Hr^{hr}/IcrCrl mice, BALB/cJ mice, treated with miR-708-NP (1.58 mg/kg) twice/week, for 2 weeks	293 T, MDA-MB-231, 4T1, treated with miR-708-NP (NP: 40 nM, miR-708: 0.24 mmol/L)	NNAT	miR-708 could ameliorate TNBC via impairing metastasis.	[41]
TNBC	miR-221/222	lipid/CaP(Calcium phosphate)/miRi complex	-	SKBr-3, MCF-7, MDA-MB-231; treated with NP (miRi), 20 pmol/mL for 5 min-4 h	TIMP3, p27^{Kip1}	The mentioned NPs system via mediating the delivery of miRi-221/222 and paclitaxel could suppress tumor proliferation by targeting p27^{Kip1} and TIMP3.	[67]
TNBC	miR-200c	RGD-PEG-ECO/miR-200c nanoparticle	Female nude mice; treated with miR-200c-RGD-PEG-ECO (1 mg/kg, I.V, 1/week, for 6 weeks)	Hs578T, MDA-MB-231; treated with miR-200c-RGD-PEG-ECO (40 and 100 nM, for 4 and 48 h	ZEB1, EDB-FN, BMI1	RGDPEG-ECO/miR-200c nanoparticle could suppress TNBC tumors.	[45]
TNBC	miR-34a	cRGD-PEG/miR-34a liposomes	-	MDA-MB-231, treated with miR-34a-cRGD-PEG (100 nM), for 4 h	Notch1, Sox2, Oct4	cRGD-PEG/miR-34a liposomes could suppress tumorigenesis.	[51]

Kardani et al. have designed a nanocarrier composed of gold nanoparticles (GNPs), antagomir-155, and nucleolin specific aptamer. AuNP-Apt-anti-miR-155 has been shown to be efficiently entered the target cells leading to reduction of miR-155 levels and elevation of TP53INP1 mRNA which is a direct target of miR-155. This nanocarrier could inhibit proliferation of breast cancer cells and induce their apoptosis through enhancing expression of TP53INP1 (Fig. 3) [26]. Besides, a fabricated dextran-coated iron oxide-based nanoparticle has been successfully used for delivery of miR-29a to breast cancer cells. Results of in vitro experiments have confirmed efficient delivery of miR-29a and subsequent down-regulation of anti-apoptotic genes in breast cancer cells [59]. Additionally, miR-145 is a tumor suppressor miRNA that is suppressed in cancer and can be used as a treatment option in a variety of malignancies, including breast cancer. Chitosan polyplex nanoparticles delivered the miR-145 plasmid into MCF-7 cells. Approximately 30% less MCF-7 cell growth was seen when chitosan polyplex nanoparticles were present [49]. Table 2 shows examples for nanoparticle-mediated delivery of miRNAs for treatment of breast cancer.

4. Nanoparticle-mediated delivery of miRNAs for treatment of brain/neurological disorders

Nanoparticle-based delivery of miRNAs has been used for treatment of glioblastoma, neuropathic pain, ischemic and hemorrhagic stroke, cerebral apoplexy and traumatic brain injury (Table 3). For instance, nanoparticles have been loaded with inhibitors of miR-21, an oncogenic miRNA that is up-regulated in glioblastoma. These nanoparticles have been administered by two different delivery systems, a cationic poly (amine-co-ester) (PACE) and a peptide nucleic acid (PNA) with a block copolymer of poly(lactic acid) and hyperbranched polyglycerol (PLA-HPG). Both nanoparticles have efficiently delivered miR-21 inhibitors and resulted in up-regulation of PTEN and enhancement of apoptosis of human glioblastoma cells. Administration of miR-21 inhibitors to animals with intracranial gliomas has resulted in significant reduction of miR-21, induction of chemosensitization, and enhancement of survival [46]. Another study has shown that a combined polymeric nanotechnology for co-delivery of anti-miR-21 and miR-124 into the brain can efficiently treat glioblastoma in an orthotopic xenograft model. These polymeric nanoparticles have been decorated with Angiopep-2 peptide for the purpose of encapsulation of miRNAs via triple-interaction as well as facilitating crossing blood brain barrier. These agents could regulate the mutant RAS/PI3K/PTEN/AKT signaling pathway, decrease tumor cell proliferation, migration and invasion and reduce tumor angiogenesis [34].

Another study has shown that miR-146a-5p-loaded poly (d, L-lactic-co-glycolic acid) nanoparticles impair pain behaviors through suppression of several inflammatory pathways in microglia [39]. Besides, nanoparticle-based delivery of miR-195 has been found to be efficient for treatmnet of ischemic and hemorrhagic stroke via affectinf neurovascularizaton and neurogenesis [7].

Table 3
Nanoparticle-mediated delivery of miRNAs for treatment of brain/neurological disorders.

Diseases	miRNA	Nanoparticles	Models	Cell lines	Targets	Observation	Ref.
Glioblastoma (GBM)	miR-21	block copolymer of poly (lactic acid) and hyperbranched polyglycerol (PLA-HPG), Cationic poly (amine-co-ester) (PACE)	Male Fischer 344 rats; treated with NPs (20 μL, infusion at 0.667 μL/min)	RG2, U87; treated with 0.5 mg/mL NPs and PACE-antimiR-21 polyplexes (100 nM), 48 h, TMZ (0–160 μM)	PTEN	The combination of PLA-HPG with TMZ could lead to the inhibition of miR-21 and decrease tumor growth.	[46]
GBM	miR-21, miR-124,	polymeric nanoparticle (Ang-PEG-b-PGu and PEG-b-P(Gu/Hb), Ang-NM@Cy5-miR-NC, NM@Cy5-miR-NC	Balb/c mice, treated with Ang-NM@Cy5-miR-NC (20 μg Cy5-miR-NC/mouse) (PBS), (30 μg miRNA/mouse), I.V	U87MG, HA1800; treated with Ang-NM@ (anti-miR-21 +miR-124) and/or NM@ (anti-miR-21 +miR-124, 40.6–325 ng/mL) for 3 days	PTEN, AKT, NRAS, RRAS, PI3K, Angiopep-2,	Using polymeric NPs/miR-124 could decrease tumorigenesis.	[34]
GBM	miR-21	FA (multi-valent folate)− 3WJ (Three-way junction)-Alexa647-LNA-miR21 nanoparticles (RNPs)	GBM30 mice; treated with miR-21-FA-3WJ-Alexa647-LNA RNPs (1 μM, tail vein)	U87EGFRvIII; treated with miR-21-FA-3WJ-Alexa647-LNA RNPs (0–1000 nM), for 72 h	PTEN, PDCD4, AKT, p27, Caspase-3	miR-21-FA-3WJ-Alexa647-LNA RNPs systemic injection via targeting PDCD4 and PTEN could cause apoptosis and tumor growth regression.	[29]
Neuropathic Pain	miR-146a-5p	poly (D,L-lactic-co-glycolic acid) nanoparticle (PLGA); 146a-5p mimic loaded on PLGA-NPs	SD rats, treated with miR-146a-5p-encapsulated PLGA NP (0.035–0.17 μM), intrathecally,	BV2; transfected with miR-146a-5p mimic (10 nM)	NF-κB/p38 MAPK, IL-6, IL-1β, TNF-α, TRAF6, IRAK1	PLGA NPs loaded on miR 146–5p could ameliorate neuropathic pain via inflammatory pathways inhibition.	[39]
Ischemic & Hemorrhagic Stroke	miR-195	commercial nanoparticle (jetPEI), miR-195 mimic loaded on jetPEI	male SD rats, treated with jetPEI-miR-195 mimic (10 nmol/kg), I.V, 0–6 hr after stroke	HEK293A, SH-SY5Y, HUVECs, THP-1, miR-195 mimic (5 and 10 nM)	Sema3A, Cdc42/JNK, NF-kB, Sema3A, Bcl-2, Caspase-3, p65/52/50	miR-195 could be anti-apoptosis via Sema3A/ Cdc42/ JNK signaling inhibition and reduce inflammation and also it could be a new drug for hemorrhagic stroke and acute ischemic treatment.	[7]
Ischemic Stroke	miR-141–3p	poly (lactic-co-glycolic acid) (PLGA)	C57BL/6 male mice' treated with PLGA NPs containing PS (phosphorothioates)− 141 and PNA (peptide nucleic acid)−141 (50 μg/kg), tail vein injection, 4 h after stroke	PBMC, treated with PS −141 NPs and PNA −141 NPs (0.02–0.2 mg/)	TNF-α	Anti-miR-141 loaded on PNA or PS could be an effective treatment for ischemic stroke.	[11]
Ischemic Brain Injury, Cerebral Apoplexy	miR-124	Mal-PEG-PLGA (maleimide-poly (ethylene glycol)-poly (lacticco-glycolic acid)) nanoparticle; RVG29-miR-124 loaded on PEG-PLGA	adult SD rat, t-MCAO rat; treated with nasally miR-124 (two drops, of 5 μg/mL aqueous solution), started 7 days before modeling induction	-	RhoA	nasal delivery of RVG29-NPs-miR124 could pass from the blood-brain barrier and could help to the neurological function improvement after cerebral ischemia.	[20]
Traumatic Brain Injury (TBI)	miR-146a	miR-146a nanoparticles	SD rats; treated with miR-146a NPs (at a rate of 10 nL/s)	SH-SY5Y, BV-2; treated with miR-146a NPs (20 nM), for 48 h	NF-κB, TRAF6, IRAK1,	p5RHH + miR-146a-Cy5 could control inflammation signals in TBI by decreasing TRAF6 and IRAK1 expression and could be a new therapy for TBI.	[54]
Tuberculous Meningitis (CNS-TBM)	miR-124–3p	PLGA (poly(lactic-co-glycolic acid)) nanoparticles; miR-124–3p loaded on PLGA	-	BAA-535, 293 T, BV2; treated with miR-124–3p and NC (100 nM)	Caspase3, Bcl-2, Bcl-xl, Stat3,	Anti-miR-124 via targeting the Stat3 signaling pathway could enhance cell proliferation and decrease apoptosis.	[66]

5. Nanoparticle-mediated delivery of miRNAs for treatment of pulmonary disorders

Efficiency of nanoparticle-based miRNA delivery has been examined in the treatment of non-small cell lung cancer, acute respiratory distress syndrome, and ventilator induced lung injury (Table 4). Genistein-miR-29b-loaded hybrid nanoparticles has been shown to be a superior to individual genistein and miR-29b-loaded nanoparticles in reducing proliferation of lung cancer cells [42]. Moreover, nanoparticle-based delivery of miR-146a has been found to regulate mechanotransduction in lung macrophages and mitigate injury during mechanical ventilation [3].

6. Nanoparticle-mediated delivery of miRNAs for treatment of other disorders

Nanoparticle-based delivery of miRNAs has also been used for treatment of a variety of malignant and nonmalignant conditions, including squamous cell carcinoma, melanoma, renal cell carcinoma, cervical cancer, prostate cancer, perinatal inflammation and atherosclerosis (Table 5). Photocontrolled miR-148b nanoparticles have been found to induce apoptosis, inflammatory responses and regression of Ras-associated epidermal squamous cell carcinomas in animal models [33]. Moreover, nanoparticle-based delivery of miR-21–3p could sensitize melanoma to anti-PD-1 immunotherapy via enhancemnet of promoting ferroptosis [19]. Besides, delivery of anti-miR-712 to inflamed endothelial cells by means of poly (β-amino ester)

Table 4
Nanoparticle-mediated delivery of miRNAs for treatment of pulmonary disorders.

Diseases	miRNA	Nanoparticles	Models	Cell lines	Targets	Observation	Ref.
Non-Small Cell Lung Cancer (NSCLC)	miR-29b	Mucin-1 (MUC1)-aptamer hybrid nanoparticles, miR-29b loaded nanoparticles, Genistein-loaded nanoparticles; genistein-miR-29b-loaded hybrid nanoparticles (GMLHN)	-	A549, MRC-5, treated with GMLHN (miR-29 (50 nM) and (genistein) 1.6 M)	AKT, PI3K, DNMT3B MCL1,	GMLHN could be a new treatment for NSCLC via inducing an anti-cancer effect.	[42]
Acute Respiratory Distress Syndrome (ARDS)	miR-146a	lipid nanoparticles (LNPs); miR-146a loaded on LNPs	Human, miR-146a knockout (KO) mice, wild-type (WT) mice, WT C57Bl/6 J mice treated with miR-146a-loaded LNPs	alveolar macrophages, THP-1, Primary polymorphonuclear cell; treated with LNPs-miR-146a (200 nM) for 24 h	IL6/8, CXCL1/KC, SMAD4	miR-146a-loaded LNPs could decrease and mitigates lung injury during mechanical ventilation.	[3]
Ventilator Induced Lung Injury (VILI)	miR-146a	Liposomes; miR-146a loaded on lipoplexes	Human, miR-146a knock-out (KO) mice, C57Bl/6 J mice, treated with miR-loaded lipoplexes (50 μL)	Human alveolar macrophages (AMs), THP-1; treated with 5 nM pre-miR-146a	IL-6/8, CXCL1/KC	miR-146a loaded on liposomal nanoparticles could limit VILI.	[2]

Table 5
Nanoparticle-mediated delivery of miRNAs for treatment of other disorders.

Diseases	miRNA	Nanoparticles	Models	Cell lines	Targets	Observation	Ref.
Epidermal Squamous Cell Carcinomas	miR-148b	Silver nanoparticles (SNPs)**;** SNP-DA (furan-maleimide Diels-Alder**)-**miR148b	C57/BL6 mice, treated with miR148b-SNP-DA (3.2 mg/Kg), I.V	PAM212; treated with SNP-DA-miR148b (5 ppm), for 3 h	ALCAM, ROCK1, NRP1, WNT1, Caspase-3	miR148b-SNP-DA via controlling the delivery of miR-148b mimic could lead to apoptosis.	[33]
Melanoma	miR-21–3p	miR-21–3p-AuNp	C57BL/6 mice, treated with miR-21–3p-AuNp (10 mg/kg, I.P), every 3 days, for 16 days	WM793B, A2058, A375, Hs294T, B16F10, treated with agomiR-21–3p (100 nM)	TXNRD1, IFN-γ, PTGS2	miR-21–3p-AuNp via TXNRD1 inhibition could elevate the sensitization of melanoma to anti-PD-1 immunotherapy.	[19]
Renal Cell Carcinoma (RCC)	miR-454–3p	Zinc oxide nanoparticles (ZONs)	Human, female BALB/c nude mice, treated with ZONs (5 mg/kg), S.C injection,	786-O, 769 P; treated with ZONs (20 μg/mL)	ACSL4, TGF-β	ZONs could suppress RCC cell oxidation, proliferation, and lipid synthesis via increasing miR-454–3p levels and ACSL4 inhibition.	[65]
Cervical Cancer	miR-29b	R11-SSPEI nanoparticles; miR-29b mimics loaded on R11-SSPEI nanoparticle	Nude (nu/nu) mice; treated with miR-29b-R11-SSPEI/Scr [5 mg/kg (5 doses, each dose administrated 2/week)]	HCvEpC, Siha, HeLa, Me 180, C-33A, Caski; treated with miR-29b-R11-SSPEI (10 nM), for 24 h	PTEN, AKT, p38/MAPK, ATM, FAM, H2AX, CHK2, p38, RAD51	miR-29b could increase radiosensitivity and decrease PTEN by inhibiting the double-strand break (DSB) repair.	[62]
Prostate cancer	miR-221/222	PEG (polyethylene glycol)-PEI (polyethylenimine), PEG-PEI/miR-221/222	-	PC-3, treated with PEG-PEI (0–300 μg/mL)/miR-221/222 (100 mM)	SIRT1	PEGPEI/miR-221/222 could be an effective treatment for PCa because it could modulate the SIRT1 gene expression in PCa Cells.	[5]
Prostate cancer	miR-141, miR-150, miR-375, miR-638	Polyethylenimine (PEI) nanoparticle	C57/BL6 mice, B16V mice; received B16V cells transfected by miR-150 mimic and antimiRs	PC3, DU-145, LNCaP, LOX, A375, SK-Mel-28, B16F10, B16V, treated with 50 μg antimiRs	Caspase-3, SEC23A, PHLPP1,	AntimiRs loaded on PEI could inhibit tumor growth or metastasis.	[27]
Perinatal Inflammation	miR-29b	*lipid nanoparticles (LNPs)*, miR-29b loaded on LNPs	Pregnant C3H/HeN mice; treated with LNPs-miR-29b (2.9 μg RNA/mouse, I.P)	-	SUV40H2, H4K20me3, α-SMA, MMP-9, PRMT1/5	LNPs-miR-29b via changing the expression of SUV40H2/H4K20me3 axis could be a potential therapeutic way.	[48]
Atherosclerosis	miR-181b	RGD−PFP-TNDs/miR-181b nanoparticles, poly-(glutamic acid)-g-poly-(ethylene glycol) (PEG-g-PGA), perfluoropentane-loaded nanodroplets (PFP-NDs), Arg−Gly−Asp (RGD)	-	HUVECs, THP-1, treated with RGD−PFPTNDs (10–50 μg/mL)	NF-κB, IPOA3, VCAM-1	Higher expression of miR-181b could reduce cell adhesion and consider a new treatment for TNF-α-stimulated endothelial cell damage.	[32]

(*continued on next page*)

Table 5 (*continued*)

Diseases	miRNA	Nanoparticles	Models	Cell lines	Targets	Observation	Ref.
Atherosclerosis	miR-712	Poly (β-amino ester)(pBAE) nanoparticles; anti-miR-712-NPs	male C57BL/6 mice, treated with VHPK-c-pBAE NPs [1 mg/kg, (carrying anti-miR-712)]	iMAECs, treated with pBAE NPs or VHPK-c-pBAE (50–200 nM), for 2 days	TIMP3, VHPK,	The complex of VHPK-c-pBAE- anti-miR-712-NPs could decrease the TIMP3 expression and inhibit the atherosclerosis mechanism.	[13]
Pulmonary & Cardiovascular Diseases	miR-210	Nickel nanoparticles (Nano-Ni)	C57BL/6 J mice; treated with Nano-Ni (50 μg/mouse, intratracheally)	BEAS-2B, A549, treated with Nano-Ni (0–30 μg/mL, for 3–24 h), [HIF-1α (+/+)] and knock-out [HIF-1α (-/-)], treated with Nano-Ni (20 μg/mL, for 24 h)	ATM, p53, HIF-1α, Rad52, MMP-2/9,	Nano-Ni via its effects on the Rad52/miR-210/HIF-1α axis could lead to genomic instability and DNA damage.	[37]
Inflammatory Disease	miR-451a	Biogenic nanoparticles (BiNPs); BiNP-associated miR-451a	-	Human adipose-derived mesenchymal stromal cells (MSCs), RAW264.7; treated with miR-451a inhibitor and miR-451a mimic (350 nM), for 6 h	TLR4, lin-14, TNF-α, IL-6/10	miR-451a could be responsible for immunomodulatory effects via increasing TLR4-related anti-inflammatory cytokines.	[54]
-	miR-21	Chitosan (CS)/ tripolyphosphate (TPP)/ hyaluronic acid (HA) nanoparticles (CTH NPs), CTH/miR-21 Nanoparticles	-	Human gingival fibroblasts; treated with 150, 300, and 450 pmol miR-21/ specimen, for 24 h	SMAD7, Col1A1, Col3A1, α-SMA,	CTH NPs could promote gingival fibroblast and increase cell adhesion and proliferation via miR-21 delivery to the target cells.	[55]
-	miR-31	Gold nanoparticles (GNPs); miR-31 antagomiR loaded on GNPs	-	MSCs, MG63, BMPR-2, BMP-R1A, treated with the GNPs (50 nM, 48 h)	BMP, Runx2, SMADs	antagomiR-GNPs could increase osterix expression in MSCs and osteogenesis via blocking miR-31.	[36]

nanoparticles could decrease the TIMP3 expression and inhibit the atherosclerosis mechanism [13]. Other examples are shown in Table 5.

7. Discussion

Nanoparticle-based delivery of miRNAs has been used for treatment of a variety of disorders, particularly cancers as well as ischemic stroke and pulmonary fibrosis. The wide range application of this type of therapy is based on the important roles of miRNAs in the regulation of cell behavior in physiological and pathological conditions. Besides, the ability of miRNAs to inhibit or increase expression of several genes gives them the superiority over mRNA or siRNA-based therapies. Since naked miRNAs can be rapidly degraded, the need for efficient and safe delivery of miRNAs has been sensed for many years. Nanoparticle-based delivery of miRNAs is a strategy for solving delivery challenges, increasing targeting efficacy and reducing off-target effects. Preparation of nanoparticles for miRNA delivery is mainly achieved through using protocols originally developed for drugs or other types of biomolecules [28]. Exosome-mediated delivery of miRNAs has been proved to be an efficient method [8]. Possible side effects of nanoparticles are inflammatory reactions, oxidative stress, and cell apoptosis leading to the cytotoxicity [52].

Cancer treatment is the most important field benefitted from this type of therapy. In fact, nanoparticle-based delivery of miRNAs has been used for induction of sensitivity to anti-cancer agents, modulation of tumor microenvironment to enhance the efficacy of immune responses against cancer and reduction of malignant features of cancer cells such as high proliferation capacity and invasiveness. In other pathological condition, our knowledge about the appropriateness of nanoparticle-based miRNA delivery systems is more obscure due to limited number of studies and possibly lack of appropriate systems for appraisal of system efficacy. miRNAs that are involved in the regulation of PI3K/AKT, mTOR and RAS/MAPK pathways are appropriate targets in this field.

Since a single miRNA can affect pathogenesis of several types of cancers, design of nanoparticle-based delivery systems for miRNAs that are widely involved in the pathoetiology of different cancers is an important step for the treatment a wide range of malignancies. However, prior assessment of expression profile of miRNAs in each patient is a prerequisite for inclusion of patients that benefit from each type of treatment.

In brief, our knowledge about miRNA-loaded nanoparticles is limited, and it is expected that numerous therapeutic possibilities will be revealed for miRNA-loaded nanoparticles in future.

Ethics approval and consent to Participant

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CRediT authorship contribution statement

SGF wrote the draft and revised it. MT and BMH designed and supervised the study. HS, LN, MHBM and FR collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Consent of publication

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