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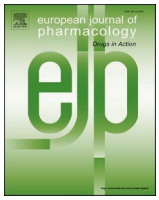

Downregulation of miR-21 as a promising strategy to overcome drug resistance in cancer

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ABSTRACT

Despite tremendous achievements in the field of targeted cancer therapy, chemotherapy is still the main treatment option, which is challenged by acquired drug resistance. Various microRNAs are involved in developing drug-resistant cells. miR-21 is one of the first identified miRNAs involved in this process. Here, we conducted a literature review to categorize different mechanisms employed by miR-21 to drive drug resistance. miR-21 targets various genes involved in many pathways that can justify chemoresistance. It alters cancer cell metabolism and facilitates adaptation to the new environment. It also enhances drug detoxification in cancerous cells and increases genomic instability. We also summarized various strategies applied for the inhibition of miR-21 in order to reverse cancer drug resistance. These strategies include the delivery of antagomiRs, miRZip knockdown vectors, inhibitory small molecules, CRISPR-Cas9 technology, catalytic nucleic acids, artificial DNA and RNA sponges, and nanostructures like mesoporous silica nanoparticles, dendrimers, and exosomes. Furthermore, current challenges and limitations in targeting miR-21 are discussed in this article. Although huge progress has been made in the downregulation of miR-21 in drug-resistant cancer cells, there are still many challenges to be resolved. More research is still required to find the best strategy and timeline for the downregulation of miR-21 and also the most feasible approach for the delivery of this system into the tumor cells. In conclusion, downregulation of miR-21 would be a promising strategy to reverse chemoresistance, but still, more studies are required to clarify the aforementioned issues.

1. Introduction

Cancer accounts for the second leading cause of death in the United States and it is proposed that 42% of men and 38% of women will be diagnosed with a type of cancer throughout their lives (Medarova et al., 2020; Siegel et al., 2020). Despite huge progress in the field of targeted cancer therapy, chemotherapy is still the main approach for cancer treatment. One of the major obstacles in chemotherapy is acquired drug resistance, which according to the literature, up to 90% of deaths among cancer patients happen due to this problem (Bukowski et al., 2020). Chemotherapy resistance is the innate or acquired ability of cancer cells to avoid the harmful effects of chemotherapeutic agents through various mechanisms (Alfarouk et al., 2015). While multiple genes implicated in drug resistance have been identified, additional genes involved in this process should still be discovered to unravel the underlying mechanisms of this phenomenon. Major mechanisms involved in drug resistance include an increase in drug efflux, a decrease in drug uptake, adjustment of drug metabolism, cell death inhibition, alteration of cell metabolism, modification of DNA repair systems, increased genomic instability and elevated tumor heterogeneity, employing cancer stem cells as the source of tumor-initiating cells, and remodeling of the tumor microenvironment to facilitate the migration of cancer cells (Bukowski et al., 2020; Phi et al., 2018). Studies have reflected that various epigenetic alterations, including DNA methylation, histone modifications, and different expression patterns of microRNAs (miRNAs), are also involved in chemoresistance (Zahan et al., 2020).

miRNAs are a group of short non-protein-coding RNAs and up to now, approximately 2600 mature miRNAs have been recognized to be encoded by the human genome (Plotnikova et al., 2019). For the first time in 2002, the relationships between microRNAs and cancer were

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identified (Calin et al., 2002). MicroRNAs can act as both oncogenes and tumor suppressor genes (Pfeffer et al., 2015) and both upregulation and downregulation of these RNAs have been reported among various types of cancers (Ali Syeda et al., 2020). The mechanisms causing the deregulation of miRNAs among cancer patients are not well understood, but both epimutations and mutations can cause this phenomenon (Ali Syeda et al., 2020). It is shown that miRNAs can target approximately 30% of human genes, and 50% of these genes are tumor-associated or are located in fragile loci, which shows they are somehow involved in tumor development and chemoresistance (Bukowski et al., 2020). Several mechanisms have been proposed to justify the contribution of miRNAs to chemotherapeutic drug resistance. They can affect cell cycle pathways and also apoptosis *via* downregulation of pro-apoptotic genes and upregulation of anti-apoptotic genes. These RNAs can improve the DNA repair system in cancer cells and protect them against mutagenesis of anti-cancer drugs, so they can help the cells to evade apoptosis in response to a high rate of DNA damage. MicroRNAs are also involved in upregulating autophagy genes, which can facilitate the ingestion and degradation of chemotherapeutic agents (Huang et al., 2020b). Moreover, they can alter cancer cell drug metabolism, which alleviates the toxicity of the drugs (Si et al., 2019). In this study, we focus on miR-21, one of the first identified microRNAs that is involved in both oncogenesis and chemoresistance (Harrandah et al., 2018a).

2. The physiological function of miR-21

MicroRNA-21 is an evolutionary conserved RNA among a great number of vertebrates (Feng and Tsao, 2016). The function of this RNA begins at the earliest stage of life. During development, miR-21 has higher expression throughout the transition of the zygote to the eight-cell stage (Mondou et al., 2012; Salilew-Wondim et al., 2020) and it is also important for embryo implantation and pregnancy preservation. It is assumed as one of the active pregnancy markers, which are expressed only among viable embryos (Reza et al., 2019). miR-21 is expressed in a wide range of human tissues and it is also involved in various important cell functions, including proliferation, growth, migration, differentiation, apoptosis, etc. miR-21 knockout mice show a higher rate of apoptosis and a lower rate of proliferation and tumorigenesis (Ma et al., 2011). It is also important for the appropriate function and homeostasis of hematopoietic stem cells, tooth development, and osseous tissue (Hu et al., 2021; Schwarze et al., 2021; Smieszek et al., 2020). miR-21 contributes to the migration and differentiation of endothelial cells and it is also involved in angiogenesis (Krzywińska et al., 2020). In the heart, miR-21 has cell type-specific functions. Although it can increase hypertrophy and fibrosis of fibroblasts, it can prevent hypertrophy and apoptosis of cardiomyocytes (Kura et al., 2020). It was shown that during inflammation, telocytes enhance angiogenesis through miR-21-3p (Zhou et al., 2019). Furthermore, studies on animal models, demonstrated that miR-21 is important for gametogenesis. For instance, miR-21 is among RNAs that are upregulated during the development of porcine oocytes (Salilew-Wondim et al., 2020); and a study on bovine samples also demonstrated that miR-21 can prevent apoptosis of cumulus cells (Salilew-Wondim et al., 2020). In addition, this RNA is also involved in the survival and proliferation of male spermatogonial cells (Reza et al., 2019).

3. Contribution of miR-21 to development of drug resistance

miR-21 is involved in all carcinogenesis phases including initiation, promotion, progression, and metastasis (Bautista-Sánchez et al., 2020). One of the crucial factors for cancer initiation is genomic instability that can be generated through telomere dysfunction and deficient DNA repair systems (Ferguson et al., 2015). Studies have shown that miR-21 can affect both of these systems. Cancer stem cells (CSCs) are also involved in cancer initiation and miR-21 is one of the major upregulated miRNAs in these cells (Harrandah et al., 2018b). Studies have shown that upregulated miR-21 in CSCs is involved in the process of reactive oxygen species (ROS) production in these cells. miR-21 can induce ROS production through the MAPK signaling pathway and downregulation of *SOD2*, *SOD3*, and *SPRY2* (Lin, 2019). *SOD2* and *SOD3* encode superoxide dismutases and can protect cells against oxidative damage (Kim et al., 2014), and *SPRY2* acts as a tumor suppressor gene and can trigger cancer cell apoptosis *via PTEN* activation and RAS-RAF-ERK inhibition (Feng et al., 2012). In total, several mechanisms are imposed for supporting the function of miR-21 in these cancer progenitor cells: miR-21 might release growth factors, which enhance stem cells; it might contribute to self-renewal of stem cells or it could induce dedifferentiation of adult cells to progenitor cells to maintain the supply of progenitor cell population (Sekar et al., 2016). miR-21 is also involved in cancer progression and metastasis. It can ensure metastasis by facilitating epithelial-mesenchymal transition (EMT) in various types of cancers.

miR-21 is also involved in the development of resistance to chemotherapeutic agents through various strategies, which is the focus of this review and will be discussed in this section.

3.1. Increase in drug efflux

Experiments on renal cell carcinoma have shown that silencing miR-21, downregulates the expression of *ABCC3-6* in RCC10 (a human renal cancer cell line), *ABCC2-6* in 786-O (a human renal adenocarcinoma cell line) and *ABCC3* and *ABCC5* in ACHN (a human renal adenocarcinoma cell line) (Gaudelot et al., 2017). In cancer cells, ABC transporters act as drug exporters, and upregulation of these proteins reduces the concentration of chemotherapeutic agents within the cells and as a result, protects them against the cytotoxicity of the drugs (Muriithi et al., 2020). A study on colon cancer showed that miR-21 can inhibit *PCD4* and, since *PCD4* no longer can downregulate *ABCC5,* a high level of *ABCC5* leads to fluorouracil-resistance in colon cancer cells (Wu et al., 2015a). Additionally, investigating miR-21 knockdown in a human lung cancer cell line indicated decreased expression of *MDR1*, demonstrating that miR-21 upregulates *MDR1*, which results in cisplatin-resistance (Dong et al., 2015b).

3.2. Decrease of drug uptake

miR-21 can reduce cellular drug uptake and prevent the accumulation of chemotherapeutic agents within the cells. It was shown that the downregulation of miR-21 in doxorubicin-resistant human hepatocellular carcinoma cells could reduce chemoresistance through escalating chemotherapy drug uptake (Wang et al., 2018). Experiments on renal cell carcinoma have indicated that silencing miR-21 upregulates the expression of some transporters including *SLC22A1*, *SLC22A2*, and *SLC31A1* (Gaudelot et al., 2017). *SLC22A1* and *SLC22A2* are both cation transporters, which can accumulate chemotherapeutic drugs within cancerous cells and, as a result, they can enhance cellular sensitivity to platinum-based drugs, including cisplatin, oxaliplatin, and picoplatin (Li and Shu, 2014; Samodelov et al., 2020). Furthermore, *SLC31A1* is also important for the uptake of platinum drugs such as cisplatin and carboplatin by cancer cells (Cheng et al., 2020).

3.3. Adjustment of drug metabolism

Glutathione S-transferases (GSTs) are one group of enzymes involved in drug detoxification and high expression of these enzymes is associated with multi-drug resistance (Mansoori et al., 2017; Singh and Reindl, 2021). They can directly detoxify anti-cancer drugs or indirectly modulate the MAPK pathway, which is important in several cellular functions such as proliferation and apoptosis (Mansoori et al., 2017). Depending on cell type and stimulus, the MAPK pathway can act as either an activator or an inhibitor of apoptosis (Yue and López, 2020). Experiments on a human lung cancer cell line (A549/DDP) showed that downregulation of miR-21 reduces the expression level of GSTs (Dong

et al., 2015b). In addition, human UDP-glucuronosyltransferase (*UGT*) enzymes are also involved in cancer drug inactivation *via* glucuronidation (Allain et al., 2020). Studies have shown that miR-21-3p can regulate the expression level of UGT1As in LS180 (a human colon adenocarcinoma cell line) and human hepatocytes (Gomes et al., 2019; Meng et al., 2021).

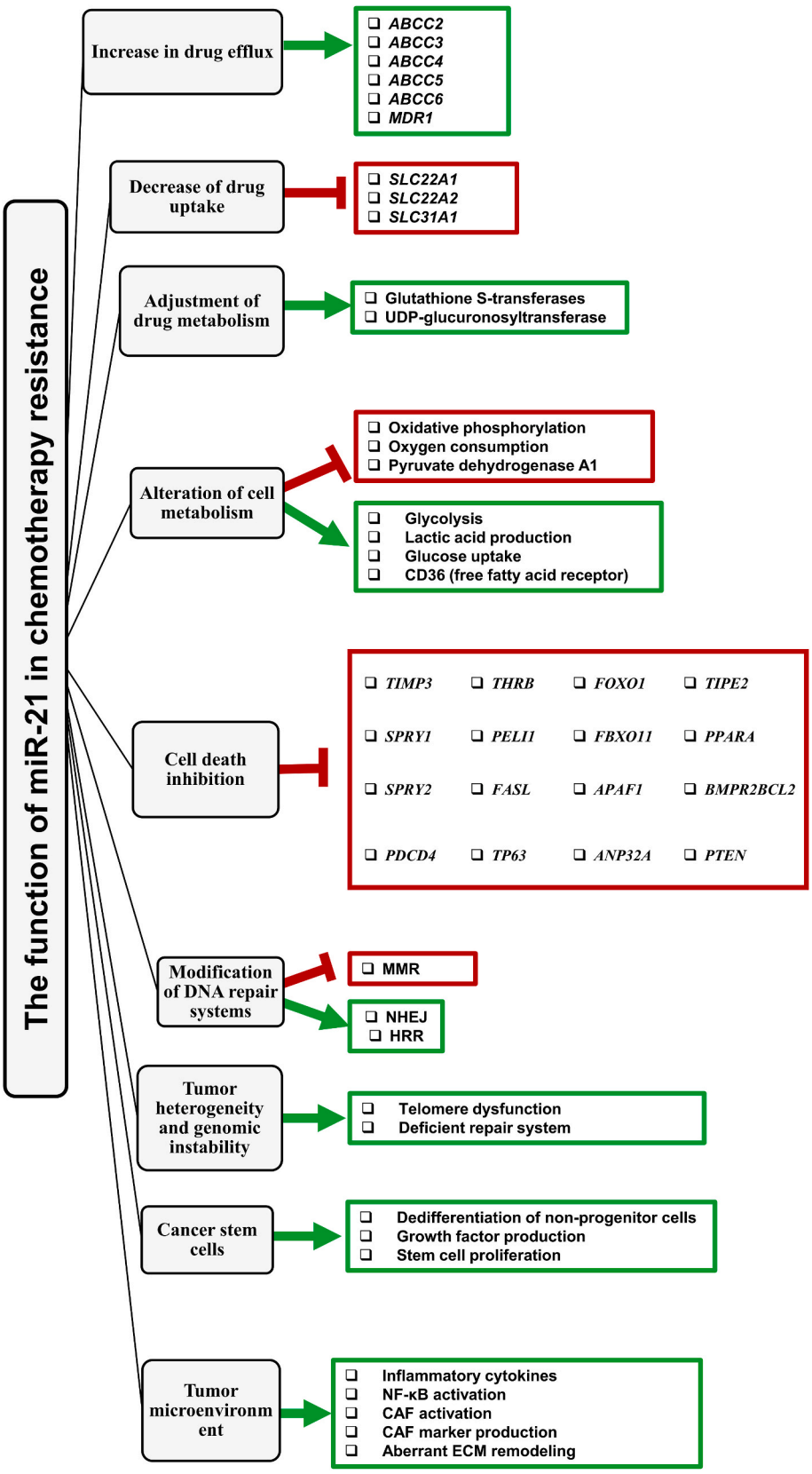

Fig. 1. The contribution of miR-21 in the development of chemotherapy resistance. *ABCC2*, ATP Binding Cassette Subfamily C Member 2; *ABCC3*, ATP Binding Cassette Subfamily C Member 3; *ABCC4*, ATP Binding Cassette Subfamily C Member 4; *ABCC5*, ATP Binding Cassette Subfamily C Member 5; *ABCC6*, ATP Binding Cassette Subfamily C Member 6; *MDR1*, Multidrug Resistance Protein 1; *SLC22A1*, Solute Carrier Family 22 Member 1; *SLC22A2*, Solute Carrier Family 22 Member 2; *SLC31A1*, Solute Carrier Family 31 Member 1; *TIMP3*, Tissue Inhibitor of Metalloproteinases 3; *SPRY1*, Sprouty RTK Signaling Antagonist 1; *SPRY2*, Sprouty RTK Signaling Antagonist 2; *PDCD4*, Programmed Cell Death 4; *THRB*, Thyroid Hormone Receptor Beta; *PELI1*, Pellino E3 Ubiquitin Protein Ligase 1; *FASL*, FAS Ligand; *TP63*, Tumor Protein P63; *FOXO1*, Forkhead Box O1; *FBXO11*, F-Box Protein 11; *APAF1*, Apoptotic Peptidase Activating Factor 1; *ANP32A*, Acidic Nuclear Phosphoprotein 32 Family Member A; *TIPE2*, Tumor Necrosis Factor, Alpha-Induced Protein 8-Like Protein 2; *PPARA*, Peroxisome Proliferator Activated Receptor Alpha; *BMPR2*, Bone Morphogenetic Protein Receptor Type 2; *BCL2*, B-Cell Lymphoma 2; *PTEN*, Phosphatase and Tensin Homolog; NHEJ, Non-homologous end joining; HRR, Homologous recombination repair; MMR, DNA mismatch repair; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; CAF, Cancer-associated fibroblast; ECM, Extracellular matrix.

3.4. Alteration of cell metabolism

Most cancer cells harbor some metabolic characteristics, that enable them to survive in the tumor microenvironment and evade chemotherapeutic agents. miR-21 is involved in multiple mechanisms that lead to the metabolic plasticity of cancer cells (Desbats et al., 2020). For instance, an investigation on non-small-cell lung carcinoma (NSCLC) proved that miR-21 promotes glycolysis and lactate production and reduces the level of oxidative phosphorylation and oxygen consumption (Dai et al., 2017a); and in cancer-associated fibroblasts, it increases glucose uptake and production of lactic acid (Chen et al., 2018b). Furthermore, in lung cancer, miR-21 induces the expression of CD36, a fatty acid receptor that acts as a translocase and affects the lipid metabolism of cancer cells (Azizi et al., 2021). In addition, in gastric cancer, high levels of miR-21 reduce pyruvate dehydrogenase A1, which couples glycolysis with the tricarboxylic acid cycle and is important for cancer cell metabolism switch (Liu et al., 2018b).

3.5. Cell death inhibition

miR-21 exerts anti-apoptotic effects *via* targeting genes involved in apoptosis (Song et al., 2017), a summary of which is shown in Fig. 1 (Buscaglia and Li, 2011; Melnik, 2015a). Downregulation of miR-21 in gastric cancer cells could restore apoptosis of malignant cells (Gu et al., 2018). Furthermore, miR-21 was involved in developing cisplatin-resistant cells in NSCLC patients *via* targeting *PTEN*, which resulted in the inhibition of apoptosis (Papadaki et al., 2020). miR-21 could also inhibit *TP53*, one of the important tumor suppressor genes that is involved in DNA damage response and induces cell cycle arrest and apoptosis (Papagiannakopoulos et al., 2008).

3.6. Modification of DNA repair systems

In 2017, Hu et al. showed that miR-21 could enhance the repair of double-strand breaks through both non-homologous end joining (NHEJ) and homologous recombinational repair (HRR) pathways and as a result, it is involved in the radioresistance of cancer cells (Hu et al., 2017). Moreover, in colorectal cancer, miR-21 was involved in developing fluorouracil-resistant cells through the reduction of *MSH2* and *MSH6* genes, which contribute to the mismatch repair system, and as a result, G2/M arrest does not happen, and apoptosis would be inhibited (Melnik, 2015a; Natarajan, 2016; Svrcek et al., 2013).

3.7. Tumor heterogeneity and genomic instability

According to previously described mechanisms, miR-21 can enhance genomic instability, which subsequently increases the risk of mutations. If mutations happen in chemotherapy target genes, the risk of drug resistance will rise (Báez-Vega et al., 2016; Melnik, 2015b).

3.8. Cancer stem cells

Cancer stem cells are clinically important, as they are resistant to various chemotherapeutic agents. In fact, miR-21 is the most reported miRNA in the regulation of colon CSCs. In colon cancer and hepatocellular carcinoma, miR-21 contributed to the regulation of stemness *via* affecting *TGFBR2* and *JAG1*, respectively (Sekar et al., 2016; Yoshida et al., 2021). Several mechanisms of action have been proposed for the contribution of miR-21 in the enrichment of CSCs. This RNA can act both on stem cells and non-progenitor cells. In non-progenitor cells, miR-21 can either trigger dedifferentiation or reinforce the expression of growth factors and subsequently, strengthen the stem cell population and can enhance CSC self-renewal (Sekar et al., 2016).

3.9. Tumor microenvironment

In the tumor microenvironment, microvesicles and exosomes play an important role in intercellular communications and, especially the delivery of miRNAs between different cell types. For example, microvesicle-mediated delivery of miR-21 from cancer cells to macrophages leads to activation of the NF-κB pathway and also the production of inflammatory cytokines like IL-6 which subsequently enhances the chance of metastasis (Pan et al., 2020). Other studies have shown that in gastric cancer, the transfer of macrophage-derived exosomal miR-21 to cancer cells leads to regulation of the PTEN/PI3K/AKT signaling pathway and, as a result, it decreases the effects of cisplatin on these cancerous cells (Shen et al., 2014; Zheng et al., 2017).

Cancer-associated fibroblasts (CAFs) are spindle-like stromal cells located in the tumor microenvironment. Based on origin and surface markers, they are heterogenous, and based on tumor type, they have different mechanisms of action in inducing drug resistance (Zhao et al., 2021a). For instance, in NSCLC, CAFs are involved in drug resistance through enhancing metabolic reprogramming, extracellular matrix remodeling, and maintenance of CSC stemness (Chen et al., 2021). CAFs can secrete chemokines and cytokines like IL-6 in gastrointestinal cancers, which results in a poor response to chemotherapy among patients. They can produce growth factors involved in cell-cell communications. CAFs can also produce exosomes, which contain long non-coding RNAs involved in drug resistance (Ham et al., 2021). In ovarian cancer, CAF-derived exosomal miR-21 was involved in paclitaxel resistance by targeting *APAF1* (Yang et al., 2017a). Altogether, studies have shown that miR-21 plays an important regulatory function in the activation of CAFs; for instance, in pancreatic ductal adenocarcinoma, miR-21 contributed to the development of drug resistance *via* triggering CAFs (Zhang et al., 2018); and in lung fibroblasts, upregulation of miR-21 led to the production of CAF markers including periostin, podoplanin, α-smooth muscle actin, and also calumenin (Kunita et al., 2018), which are associated with cell migration, metastasis, and chemotherapy resistance (Yang et al., 2021).

Aberrant extracellular matrix (ECM) remodeling in the tumor microenvironment is another important factor involved in drug resistance (Brown et al., 2019; Skhinas and Cox, 2018). The components of ECM contribute to CSC survival and maintenance of the cancer niche (Brown et al., 2019). For instance, studies on breast and ovarian cancers showed that binding of CSCs to hyaluronic acid, which is a major component of ECM, would increase the expression level of stemness-related transcription factors and also *MDR1* gene, which both could exacerbate chemoresistance (Nallanthighal et al., 2019).

The involvement of miR-21 in chemotherapeutic drug resistance *via* different mechanisms is summarized in Fig. 1.

In general, among different types of cancers, miR-21 is involved in chemotherapeutic resistance *via* altering the expression of various genes, as summarized in Table 1. Moreover, both isoforms of miR-21 can affect genes that are targeted by various chemotherapy drugs. These genes are shown in Fig. 2.

4. Strategies for downregulation of miR-21

Since miR-21 is one of the most common oncogenic microRNAs with upregulation in almost all cancer types, scientists have developed various strategies for downregulation of this RNA. Here, we focus on studies that showed downregulation of miR-21 could enhance the chemotherapeutic effects of cancer drugs *in vitro* or *in vivo*.

4.1. Use of AntagomiRs (anti-sense oligonucleotides)

AntagomiRs are synthetic antisense RNA oligonucleotides, that inhibit the binding of microRNAs to their mRNA targets. For optimizing the *in vivo* function of an anti-miR, several chemical modifications could be performed on its sugar, nucleobase, and also internucleobase

Table 1
Contribution of miR-21 tochemotherapy resistance via affecting various genes.

Cancer type	Drug resistance related to miR-21	Genes that their expression is affected by miR-21
Breast cancer	Trastuzumab (Gong et al., 2011), paclitaxel (Zhao et al., 2015), doxorubicin (Hong et al., 2013), 4-hydroxytamoxifen, topotecan (Arghiani and Matin, 2021), and fulvestrant (Yu et al., 2016b)	*PTEN* (Hong et al., 2013), *PDCD4* (Hong et al., 2013; Huang et al., 2020a; Najjary et al., 2020), *TIMP3* (Najjary et al., 2020), *FOXO3A* (Liu et al., 2015b), *ANKRD46* (Yan et al., 2011), *TGFB1* (Dai et al., 2017b), *TPM1* (Zhu et al., 2007), *BCL2* (Jahanafrooz et al., 2017), *FASLG* (Kuang and Nie, 2016), *RHOB* (Kuang and Nie, 2016), *SERPINB5* (Kuang and Nie, 2016), *RECK* (Kuang and Nie, 2016), *RTN4* (Bautista-Sánchez et al., 2020), *LZTFL1* (Wang et al., 2019), and *STAT3* (Zhang et al., 2016)
Myeloma	Bortezomib, dexamethasone, doxorubicin (Wang et al., 2011), and melphalan (Leone et al., 2013)	*PIAS3* (Xiong et al., 2012), *PTEN* (Leone et al., 2013), *AKT* (Leone et al., 2013), *STAT3* (Xiong et al., 2012), *RANKL* (Leone et al., 2013), *OPG* (Leone et al., 2013), *NF-κB* (Xiong et al., 2012), and *RHOB* (Wang et al., 2011)
Leukemia	Daunorubicin (Vandewalle et al., 2021), doxorubicin (Li et al., 2022), imatinib (Zhang et al., 2021), and cytarabine (Vandewalle et al., 2021)	*PTEN* (Wang et al., 2015a), *PDCD4* (Vandewalle et al., 2021), *BTG2* (Vandewalle et al., 2021), *TPM1* (Labib et al., 2017), *AKT* (Li et al., 2018), *ZAP70* (Carabia et al., 2017), *MAPK* (Carabia et al., 2017), and *STAT3* (Carabia et al., 2017)
Melanoma	Doxorubicin (Melnik, 2015b)	*TIMP3* (Wang et al., 2020), *PTEN* (Saldanha et al., 2016), *PDCD4* (Yang et al., 2011), *FBXO11* (Yang et al., 2015), and *TP53* (Varrone and Caputo, 2020)
Glioblastoma and glioma	Teniposide (Li et al., 2009), paclitaxel (Ren et al., 2010), fluorouracil (Moore and Zhang, 2010), sunitinib (Costa et al., 2013), temozolomide (Shi et al., 2010b), cisplatin (Sun et al., 2021), and carmustine (Wang et al., 2017)	*LRRFIP1* (Li et al., 2009), *BCL2* (Moore and Zhang, 2010), *SPRY2* (Kwak et al., 2011), *MSH2* (Maachani et al., 2016), *PDCD4* (Maachani et al., 2016), *PTEN* (Masoudi et al., 2018), *IGFBP3* (Yang et al., 2014), *RECK* (Gabriely et al., 2008), *TIMP3* (Gabriely et al., 2008), and *FASL* (Shang et al., 2015)
Gastrointestinal cancer	Cisplatin (Gu et al., 2020), doxorubicin (Chen et al., 2018a), trastuzumab (Eto et al., 2014), paclitaxel (Jin et al., 2015), and fluorouracil (Deng et al., 2014)	*PTEN* (Chen et al., 2018a), *TIMP3* (Chen et al., 2018a), *CCL20* (Vicinus et al., 2013), *ITGB4* (Ferraro et al., 2014), *TET1* (Ma et al., 2018b), *MSH2* (Deng et al., 2014), *PDCD4* (Ferraro et al., 2014), *RASA1* (Gong et al., 2015), *SPRY2* (Feng et al., 2012), *STAT3* (Tse et al., 2022), *SMAD6* (Xu et al., 2016), *SMAD7* (Jiang et al., 2018; Xu et al., 2016), and *RECK* (Zhang et al., 2008)
Hepatic cancer	Sorafenib (He et al., 2015), Fluorouracil (Tomimaru et al., 2010), cisplatin (Chen et al., 2019b), and doxorubicin (Xia et al., 2020)	*FASLG* (Chen et al., 2019b), *PTEN* (He et al., 2015; Xia et al., 2020), *AKT* (He et al., 2015), *PDCD4* (El Gedawy et al., 2017), *SOCS6* (Li et al., 2015), *RECK* (Zhang et al., 2020), *TIMP3* (Hu et al., 2016), and *NAV3* (Wang et al., 2015b)
Pancreatic cancer	Gemcitabine (Dong et al., 2011) and fluorouracil (Wei et al., 2016)	*BCL2* (Dong et al., 2011), *PTEN* (Wei et al., 2016), and *PDCD4* (Wei et al., 2016)
Lung cancer	Gefitinib (Jing et al., 2018), platinum-based drugs like cytarabine and cisplatin (Markou et al., 2016; Xu et al., 2014a)	*BCL2* (Xu et al., 2014b), *PDCD4* (Jiang et al., 2017), *PKR* (Lasithiotaki et al., 2017), *PTEN* (Xu et al., 2014b), *ERK* (Huang et al., 2021), *EGFR* (Seike et al., 2009), *SMAD7* (Li and Wu, 2018), *CASP8* (Jiang et al., 2017), *TGFB1* (Yan et al., 2018), and *RECK* (Xu et al., 2014b)
Prostate cancer	Docetaxel (Shi et al., 2010a), and doxorubicin (Zhao et al., 2021b)	*PDCD4* (Dong et al., 2015a), *BMPR2* (Qin et al., 2009), *TGFB1* (Mishra et al., 2014), *PTEN* (Yang et al., 2017b), *RECK* (Reis et al., 2012), and *TPM1* (Zhu et al., 2007)
Lymphoma	CHOP chemotherapy combination: cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (Bai et al., 2013)	*PTEN* (Song et al., 2017) and *FOXO1* (Go et al., 2015)
Neuroblastoma	Cisplatin (Chen et al., 2012)	*PTEN* (Chen et al., 2012) and *BCL2* (Chen et al., 2012)
Cervical cancer	Cisplatin (Masadah et al., 2021; Wen et al., 2017)	*PTEN* (Wen et al., 2017), *PDCD4* (Wen et al., 2017), *LATS1* (Liu et al., 2015a), and *GAS5* (Wen et al., 2017)
Bladder	Doxorubicin (Lei et al., 2015)	*PTEN* (Lei et al., 2015), *SERPINB5* (Zhang et al., 2015), and *VEGFC* (Zhang et al., 2015)
Ovarian cancer	Cisplatin and paclitaxel (Echevarría-Vargas et al., 2014; Xie et al., 2013)	*PDCD4* (Echevarría-Vargas et al., 2014)

PTEN, Phosphatase and Tensin Homolog; *PDCD4*, Programmed Cell Death 4; *TIMP3*, Tissue Inhibitor of Metalloproteinases 3; *ANKRD46*, Ankyrin Repeat Domain 46; *TGFB1*, Transforming Growth Factor Beta 1; *TPM1*, Tropomyosin 1; *BCL2*, B-Cell Lymphoma 2; *FASLG*, FAS Ligand; *RHOB*, RAS Homolog Family Member B; *SERPINB5*, Serpin Family B Member 5; *RECK*, Reversion Inducing Cysteine Rich Protein With Kazal Motifs; *RTN4*, Reticulon 4; *LZTFL1*, leucine zipper transcription factor like 1; *STAT3*, signal transducer and activator of transcription 3; *PIAS3*, protein inhibitor of activated STAT 3; *AKT*, AKT serine/threonine kinase 1; *RANKL*, Receptor Activator of Nuclear Factor Kappa-B Ligand; *OPG*, Osteoclastogenesis Inhibitory Factor; *NF-κB*, Nuclear Factor Kappa-B; *BTG2*, BTG anti-proliferation factor 2; *ZAP70*, Zeta Chain of T Cell Receptor Associated Protein Kinase 70; *MAPK*, Mitogen-Activated Protein Kinase 1; *FBXO11*, F-Box Only Protein 11; *TP53*, Tumor Protein P53; *LRRFIP1*, LRR Binding FLII Interacting Protein 1; *SPRY2*, Sprouty RTK Signaling Antagonist 2; *MSH2*, MutS Homolog 2; *IGFBP3*, insulin like growth factor binding protein 3; *FASL*, FAS Ligand; *CCL20*, C–C Motif Chemokine Ligand 20; *ITGB4*, Integrin Subunit Beta 4; *TET1*, Ten-eleven Translocation 1; *RASA1*, RAS p21 protein activator 1; *SMAD6*, Suppressor of Mothers Against Decapentaplegic 6; *SMAD7*, Suppressor of Mothers Against Decapentaplegic 7; *SOCS6*, Suppressor of Cytokine Signaling 6; *NAV3*, Neuron Navigator 3; *PKR*, Protein Kinase, Interferon-Inducible Double Stranded RNA; *BMPR2*, Bone Morphogenetic Protein Receptor Type 2; CHOP, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone; *FOXO1*, forkhead box O1; Large Tumor Suppressor Kinase 1; *GAS5*, Growth Arrest Specific 5; *SERPINB5*, serpin family B member 5; *VEGFC*, Vascular Endothelial Growth Factor C.

interactions (Stenvang et al., 2012a, 2012b). In a cisplatin-resistant ovarian cancer cell line (A2780), co-delivery of anti-miR-21 and cisplatin using a polyethylene glycosylated nanoparticle with an aptamer as a targeting molecule could increase the mortality rate of cancer cells (Vandghanooni et al., 2018). Moreover, the application of anti-miR-21 and 5-fluorouracil *via* targeted exosomes could effectively overcome drug resistance in colon cancer cells both *in vitro* and *in vivo* (Liang et al., 2020).

4.2. miRZip knockdown vectors

Engineered lentiviral and adeno-associated viral (AAV) vectors have been successfully used for the expression of antisense RNA against miR-21 (miRZip-21) (Bhere et al., 2020). miRZip hairpins were designed asymmetrically for preferentially producing antisense RNA complementary to the microRNA (Huang et al., 2013). Huang et al. applied lentiviral vectors expressing miRZip-21 on radioresistant esophageal squamous cancer cells (TE-1), which could increase the radiosensitivity of these cells (Huang et al., 2013). In 2020, Bhere et al. applied lentiviral and AAV vectors expressing miRZip-21 and at the same time AAV-miR-7

to downregulate miR-21 and upregulate miR-7, respectively, in a broad spectrum of cancer cells. They showed an increased apoptosis rate and reduced cell proliferation, invasion, and migration *in vitro,* and the therapeutic effects were also significant *in vivo* (Bhere et al., 2020).

4.3. Application of small molecules

Scientists have found several small molecules that can modify the activity of miRNAs (Fan et al., 2019). By applying functional assays and screening small molecule libraries, these modifiers could be identified (Connelly and Deiters, 2014). For the first time in 2008, Gumireddy et al. applied a luciferase-based cellular assay and identified the first small molecule that acts as a miR-21 inhibitor (diazobenzene) (Gumireddy et al., 2008). Other small molecules with inhibitory effects on miR-21 include streptomycin, 6-hydroxy-DL-DOPA, AC1MMYR2, 3, 3′diindolylmethane (DIM) and ALWPPNLHAWVP (Nikulin et al., 2020; Wen et al., 2015).

In 2018, Naro et al. investigated 1,2,4-oxadiazole miR-21 inhibitor 37 on a chemoresistant renal cell carcinoma cell line (A498). This type of cancer is generally resistant to topotectan, which is a chemotherapeutic agent. The results indicated a more than 11-fold increase in drug potency in comparison to the solo application of topotecan (Naro et al., 2018). Furthermore, in 2020, scientists used a natural substance, which can be found in some vegetables and acts as a miR-21 antagonist (DIM). They cultured organoids from metastatic breast cancer patients, and tested the effects of DIM alongside the combined treatment of cyclophosphamide and methotrexate. They confirmed that miR-21-5p was suppressed and subsequently, the susceptibility of cancer cells to combined treatment had risen significantly (Nikulin et al., 2020).

4.4. CRISPR-Cas9 technology

Since the introduction of the CRISPR-Cas9 system, this genome-editing tool was primarily applied to protein-coding genes, but as it progressed, the knockout of non-coding genes was also feasible. In 2015, Ho et al. produced various human cell lines encompassing knockout miR-21 *via* the homologous recombination-mediated method of the CRISPR-Cas9 system (Ho et al., 2015). In 2017, scientists designed lentiviral CRISPR/Cas9 vectors to induce mutations in pre-miR-21 sequences in ovarian cancer cell lines (SKOV3 and OVCAR3). Their experiment resulted in the upregulation of an epithelial cell marker (E-cadherin) and downregulation of mesenchymal markers (Vimentin and SNAI2). The change in the pattern of expression of these markers reflected a reduction in epithelial-mesenchymal transition. They also observed a significant reduction in migration, proliferation, and invasion, and also an enhancement in paclitaxel response (Huo et al., 2017).

Up to now, with the application of CRISPR-Cas9 system, two studies have suggested that miR-21 knockout could improve the sensitivity of cancer cells to chemotherapeutic agents through inhibition of the PI3K/AKT signaling pathway. In the first study, application of lentiviral CRISPR-Cas9 system on a nasopharyngeal carcinoma cell line (CNE2) resulted in a lower rate of migration and invasion and also induction of apoptosis through inhibition of the PI3K/AKT/mTOR signaling pathway. In the second experiment, miR-21 was knocked out in an imatinib-resistant human leukemia cell line (563/G01). In the latest study, activation of PI3/AKT signaling and cell proliferation were inhibited and the expression level of BCR-ABL was also reduced and as a result, cancer cells showed increased imatinib sensitivity (Zhang et al., 2021).

4.5. Catalytic nucleic acids

Catalytic nucleic acids including hammerhead ribozymes and DNAzymes are generally used for messenger RNA inhibition, but in 2016, Belter et al. reported their application for effective inhibition of miR-21 in glioma cells (T98G) (Belter et al., 2016). Then, Larcher et al. introduced RNV541, a novel DNAzyme which was coalesced with a transferring receptor targeting aptamer for targeted inhibition of miR-21 in glioma cells (U87MG) and also in a breast cancer cell line (MDA-MB-231) with 90% and 50% efficiency, respectively (Larcher et al., 2019). One of the advancements in this field was achieved by Liu et al. in 2021. They designed a photo-controlled DNAzyme with the ability to target endogenous miR-21. In their study, applying MnO_2 nanosheets for the protection of DNAzymes from enzymatic digestion could enhance the efficiency of miR-21 inhibition (Liu et al., 2021b).

4.6. Artificial RNA and DNA sponges

MicroRNA sponges are synthetic circular RNAs consisting of repeated miRNA antisense sequences that provide multiple miR binding sites and could absorb the target miRNAs like a sponge. Since binding sites are complementary to the seed sequence, they can inhibit multiple members of miRNAs in a seed family (Ebert and Sharp, 2010; Kluiver et al., 2012; Rossbach, 2019). In 2018, the first application of miR-21 sponge in gastric cancer cells was reported and could successfully suppress cancer cell proliferation (Liu et al., 2018a). Geo et al. applied

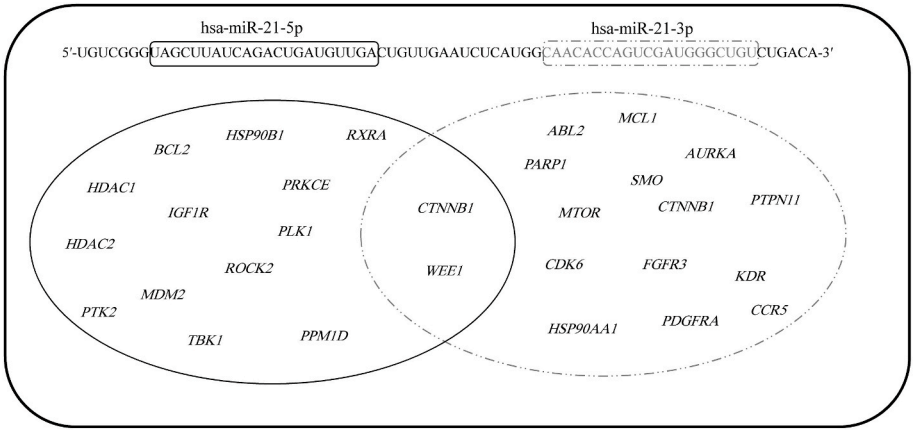

Fig. 2. miR-21 targets genes which are also targeted by chemotherapy drugs. This figure is obtained by a comparison between a gene list from the CancerDR database and target genes of each isoform from DIANA-TarBase v8 (Karagkouni et al., 2018; Kumar et al., 2013). *BCL2*, B-cell Lymphoma 2; *HSP90B1*, Heat Shock Protein 90 Beta Family Member 1; *RXRA*, Retinoid X Receptor Alpha; *HDAC1*, Histone Deacetylase 1; *PRKCE*, Protein Kinase C Epsilon; *IGF1R*, Insulin Like Growth Factor 1 Receptor; *PLK1*, Polo Like Kinase 1; *CTNNB1*, Catenin Beta 1; *HDAC2*, Histone Deacetylase 2; *ROCK2*, Rho Associated Coiled-Coil Containing Protein Kinase 2; *WEE1*, WEE1 G2 Checkpoint Kinase; *MDM2*, Mouse Double Minute 2 Homolog; *PTK2*, Protein Tyrosine Kinase 2; *TBK1*, TANK Binding Kinase 1; *PPM1D*, Protein Phosphatase, Mg^{2+}/Mn^{2+} Dependent 1D; *PARP1*, Poly(ADP-Ribose) Polymerase 1; *ABL2*, Abelson-Related Gene Protein; *MCL1*, Myeloid Cell Leukemia 1; *SMO*, Smoothened, Frizzled Class Receptor; *AURKA*, Aurora Kinase A; *MTOR*, Mammalian Target of Rapamycin; *CTNNB1*, Catenin Beta 1; *PTPN11*, Protein Tyrosine Phosphatase Non-Receptor Type 11; *CDK6*, Cyclin Dependent Kinase 6; *FGFR3*, Fibroblast Growth Factor Receptor 3; *KDR*, Kinase Insert Domain Receptor; *HSP90AA1*, Heat Shock Protein 90 Alpha Family Class A Member 1; *PDGFRA*, Platelet Derived Growth Factor Receptor Alpha; *CCR5*, C–C Motif Chemokine Receptor 5.

cationic polymers (poly-L-lysine (PLL) and polyethylenimine (PEI)) for transfecting a DNA plasmid encoding miR-21 sponge into MCF-7 cells that could sensitize cancer cells to doxorubicin and cisplatin (Lin et al., 2018a). Furthermore, Zhang et al. produced DNA nanosponges with MUC1 aptamer, antisense miR-21, and doxorubicin binding sites. Their construct showed a cell-type specific effect and it could synergistically enhance the cytotoxicity of doxorubicin on MCF-7 cancerous cells, while it had less effects on normal cells due to the application of MUC1 aptamer for targeted delivery of the sponge to the cancerous cells (Zhang et al., 2019).

4.7. Nanostructures

The advent of nanotechnology has provided a great platform in the field of targeted drug delivery, combinational therapy, and microRNA-delivery systems (Fu et al., 2019; Iranpour et al., 2021). Here, we describe the application of various types of these nanostructures.

4.7.1. Liposomes

Liposomes are the first approved nano-vehicles used in cancer treatment. These nanoparticles are biodegradable, biocompatible, and non-toxic phospholipid bilayers with both non-polar and aqueous cavities that enable them to load both hydrophobic and hydrophilic drugs. Surface modifications such as polyethylene glycol (PEG) can decrease blood clearance and enhance their circulation time. Moreover, conjugation with bio-materials including antibodies, glucose, folic acid, and aptamers can be applied in targeted drug delivery of liposomes. There are also theranostic liposomes with imaging agents that can be used to improve therapeutic applications. The majority of miR-21 delivery studies by liposomes have been designed based on lipoplexes that are cationic liposomes suitable for cytoplasmic delivery of particles with a negative charge such as DNA or RNA (Zhang et al., 2012). Costa et al. applied lipoplex for downregulation of miR-21 in glioblastoma cells and examined the efficacy of an antiangiogenic drug (sunitinib). The lipid composition of lipoplex was a combination of di-octadecyl-amidoglycyl-spermine (DOGS), dioleoylphosphatidylethanolamine (DOPE), and anti-miR-21 oligonucleotide that was labeled with a fluorescent dye. This method could enhance the cytotoxicity of sunitinib and reduced tumor cell proliferation (Costa et al., 2013).

4.7.2. Mesoporous silica nanoparticles (MSNs)

MSNs are biocompatible porous structures with thermal stability and desirable surface features for performing various modifications. Since the introduction of MSNs in 1992, great interest has been attracted to the application of these particles in the field of drug delivery and also miRNA delivery (Fu et al., 2019; Iranpour et al., 2021; Jafari et al., 2019). Hu et al. modified the surface of MSNs with PEI and conjugated the particles with hyaluronic acid as a targeting molecule for down-regulation of miR-21, and could enhance the therapeutic effects of resveratrol on two human gastric cancer cell lines, including BGC823 and SGC-7901. Resveratrol is a non-chemotherapeutic substance with an anticancer effect widely used in Chinese medicine. This method could significantly increase the anti-cancer efficacy of resveratrol on both cancer cell lines (Hu et al., 2019). In 2016, MSNs were coated with cell-penetrating poly (disulfide)s and DEVD-AAN and loaded with Ant21 (a chemically modified ASO for downregulation of miR-21) to down-regulate miR-21 in HeLa cells, and Ant21 was encapsulated by gefitinib, dasatinib, and olaparib. This technique resulted in rapid cellular uptake and successful combinational therapy and provided a new approach for detecting real-time drug release (Yu et al., 2016a). Khatami et al. coated MSNs with chitosan, a non-toxic linear polysaccharide, and AS1411 aptamer as a targeting molecule against nucleolin, which is a protein highly expressed in several types of cancers. They investigated the effects of the nanoparticle on three nucleolin-expressing cancer cell lines (C26; mouse colorectal cancer, 4T1; mouse breast cancer, and MCF-7) and a nucleolin-negative cell line (CHO; Chinese hamster ovary). Their experiment showed enhanced drug cytotoxicity on nucleolin-positive cells, while no toxic effects were observed in nucleolin-negative cells, which illustrated the successful targeted delivery of the nanoparticle (Khatami et al., 2021).

4.7.3. Dendrimers

Dendrimers are biodegradable macromolecules with a central core and lots of branches that provide binding capacity for oligonucleotides and drug molecules (Liu et al., 2021a; Sato and Anzai, 2013). Several dendrimers with potential for drug delivery include poly (amidoamine) (PAMAM) dendrimers, poly(propyleneimine) (PPI) dendrimers, Frechet-type dendrimers, peptide dendrimers, glycodendrimers, hybrid dendrimers, polyester dendrimers, poly-L-lysine (PLL) dendrimers, and carbosilane dendrimers (Santos et al., 2019).

Various innovations and modifications have been introduced to enhance the effectiveness of dendrimers in the downregulation of miR-21. Wang et al. applied modified nano-graphene oxide with polyethylene glycol and low molecular weight PAMAM dendrimer for *in vitro* and *in vivo* experiments on NSCLC cells, and for monitoring the delivery, they applied a luciferase reporter. Although they did not use any therapeutic agents, they got higher transfection efficiency, lower cytotoxicity, and stronger inhibition of cell migration and metastasis in comparison to bare dendrimer (Wang et al., 2016). In another study on pancreatic cancer, which is known for the low permeability of cancerous tissue to chemotherapeutic agents, an ultrasound-targeted microbubble destruction (UTMD)-promoted delivery system was designated as a strategy for increasing cell permeability and drug uptake. They applied dendrimer-entrapped gold nanoparticles (AuDENPs) for the co-delivery of gemcitabine and the miR-21 inhibitor. Their study resulted in a significant reduction of tumor volume and enhanced blood perfusion of pancreatic tumors *in vivo* (Lin et al., 2018b). In 2020, the same group developed core-shell tecto dendrimers (CSTDs) which function similar to high-generation PAMAM dendrimers and consisted of G5 PAMAM dendrimers as the core, surrounded by 4.2 G3 dendrimers. This strategy was applied for the co-delivery of doxorubicin and miR-21i to MDA-MB-231 cells (a human breast cancer cell line) and resulted in a significantly enhanced therapeutic efficacy of doxorubicin (Song et al., 2020).

4.7.4. Exosomes

Exosomes are small membrane-bound particles with several advantages that make them fascinating delivery vehicles. They can be loaded with abundant portions of nucleic acids, including miRNAs and lncRNAs. Exosomes are also non-immunogenic particles, owing to the fact that they can be derived from the host's own membranes (Lim and Kim, 2019). In 2019, Monfared et al. applied engineered exosomes with miR-21 sponge to glioma cell lines and also in a glioblastoma rat model. They showed a significant reduction in proliferation, and increased apoptotic rate *in vitro*, and the volume of tumors in the rat model of glioblastoma decreased significantly, which reflects successful penetration of exosomes through the blood-brain barrier (Monfared et al., 2019). Liang et al. applied engineered exosomes for targeted co-delivery of 5-fluorouracil and a miR-21 inhibitor oligonucleotide to a fluorouracil-resistant colon cancer cell line (HCT 116 ^{5FR}). Previous studies have shown that in colon cancer, miR-21 can cause 5-FU-resistance *via* downregulation of *hMSH2* (Liang et al., 2020). They applied the expression of HER2-LAMP2 fusion protein on the surface of the exosomes for targeted delivery of the particles. In a co-delivery experiment, higher efficiency of fluorouracil was observed both *in vitro* and *in vivo* (Liang et al., 2020).

4.7.5. DNA nanocages

These particles are cage-like structures with a size range of 10–100 nm, and they have great potential for application in targeted delivery studies (Chandrasekaran and Levchenko, 2016). In 2021, Raniolo et al. applied an octahedral DNA nanocage for the co-delivery of doxorubicin

and miR-21 inhibitor to cervical cancer cells (HeLa) and ovarian cancer cells (IGROV1). From the assembly of eight oligonucleotides, twelve double-stranded B-DNA helices would be produced, and in total, each nanocage provided four binding sites for miR-21. Since in both cell lines the expression of folate receptor is high, they used folic acid as the targeting molecule. This method could reduce the expression of miR-21 up to 80% after two days of treatment, decrease cancer cell proliferation and migration, and enhance cancer cell death (Raniolo et al., 2021).

4.7.6. Graphene oxide-based nanocomplexes

Graphene oxide sheets could be modified with biocompatible polymers and used in drug delivery and also RNA delivery (Wu et al., 2015b). PPG, a graphene oxide-based nanocomplex, was used to reverse drug resistance in MCF-7 breast cancer cells. It consisted of PEI/poly (sodium 4-styrenesulfonate) (PSS)/graphene oxide (GO) and could deliver the molecules through caveola and clathrin-mediated endocytosis. By physical mixing of doxorubicin with the nanocomplex and loading anti-miR-21 through electrical absorption, the nanocomplex was produced. This method could enhance doxorubicin accumulation within cells and effectively reverse cancer cell drug resistance (Zhi et al., 2013).

4.7.7. High-density lipoprotein-mimicking nanoparticles (HMNs)

HMNs are biocompatible and biodegradable nanocarriers that could be used in drug delivery (Ma et al., 2018a). Rui et al. used HMNs as a carrier for co-delivery of miR-21 inhibitor and prodrug of doxorubicin in MCF-7/ADR cells (a doxorubicin-resistant breast cancer cell line). They coupled prodrug with a nuclear localizing sequence (NLS) to make a cationic complex settle inside the cavity of HMNs that harbored anti-miR-21 molecules with the negative charge on their surface and coated the particle with anionic lipids and APOA1 protein. Delivery of the drug was performed through an HDL-receptor-mediated pathway and enhanced intracellular accumulation of doxorubicin, and also effectively suppressed miR-21 in cancer cells (Rui et al., 2017).

4.7.8. Polymeric nanoparticles

Polymeric nanoparticles could be in the size range of 10–1000 nm with various polymer compositions (Zielińska et al., 2020). In 2015, PLGA-b-PEG polymer was applied for simultaneous downregulation of two miRNAs involved in chemotherapy resistance of triple-negative breast cancer cells (MDA-MB-231), i.e. miR-21 and miR-10b. For targeting molecule, uPA peptide was applied to lead the nanoparticle to cancer cells expressing urokinase plasminogen activator receptor. Although no chemotherapy was applied in this study, a considerable therapeutic effect was observed in a very low dose of anti-miR molecules that indicated a potential for combining this strategy with chemotherapeutic agents (Devulapally et al., 2015).

4.7.9. Gold nanocages

Gold nanocages are among the fascinating nanoparticles that are also compatible with application in photothermal therapy (Chen et al., 2010). In 2018, scientists combined chemotherapy, miRNA therapy, and photothermal therapy by applying gold nanocages to doxorubicin-resistant hepatocellular carcinoma cells (HepG2/ADR). They used AuNCs, which are gold nanocages with the ability to perform photothermal conversion under near-infrared light irradiation, for their study (Wang et al., 2018). Another group, working on hepatocellular carcinoma, conjugated the PEI-modified PEGylated particles with hyaluronic acid as a targeting molecule and added doxorubicin to the culture medium. This strategy led to enhanced intracellular doxorubicin accumulation within cancer cells and significantly increased sensitivity of the cells to the drug (Yan et al., 2019).

5. Potential challenges and limitations of targeting miR-21

Although miR-21 is over-expressed in most cancer cells, it is also expressed in a wide range of normal human tissues and is involved in various important cell functions, including proliferation, growth, migration, differentiation, apoptosis, etc (Feng and Tsao, 2016). Since it has physiological functions in normal cells, for inhibiting miR-21, scientists should consider that disturbance of this RNA in normal tissues can cause unpredicted health problems. Therefore, one of the most important challenges is to select the best-targeted strategy for knocking down or knocking out miR-21, in order to reduce the adverse side effects.

Since miR-21 targets many known and unknown genes in both normal and cancer tissues, and inhibition of this RNA can cause undesirable and unpredictable consequences, a comprehensive study of miR-21 target genes among various tissues and cell types is essential. miR-21 is an evolutionary conserved RNA and in some cellular stress conditions such as cardiovascular and neurological disorders, upregulation of this RNA acts as a protective mechanism for the tissue (Bai and Bian, 2022; Chen et al., 2019a). According to the protective role of miR-21, it is not clear if long-term inhibition of this miR could be beneficial. Moreover, it is not obvious whether miR-21 knockdown or knockout would be the most appropriate approach to fight against cancer. On the other hand, it is still ambiguous whether long-term inhibition of miR-21 could trigger another compensatory alternative pathway that may cause resistance to miR-21 inhibitor. Another major obstacle is that, until now, no study has investigated the proper timing of miR-21 inhibition, and it is not still clear at which stage of cancer is the efficiency of miR-21 inhibition the highest. So further studies are required to address these questions and move this strategy closer to the clinic.

6. Perspectives and conclusions

MicroRNA-21 is one of the most common upregulated oncomiRs in almost all types of cancers. It contributes to all oncogenic stages and also the development of drug resistance through various mechanisms, including decrease of drug uptake, increase in drug efflux, adjustment of drug metabolism, alteration of cell metabolism, inhibition of apoptosis, modification of DNA repair systems, tumor heterogeneity and genomic instability, fortification of cancer stem cells, and modifying tumor microenvironment. Regardless of cancer types, in all studies downregulation of miR-21, led to improvements in anti-cancer response, and in studies in which a combination of a miR-21 inhibitor and chemotherapeutic agents were investigated, the combinational therapy was more successful than monotherapy with miR-21 inhibitor or the drug, moreover, modulation of miR-21 along with tissue-specific microRNAs could also enhance therapeutic efficacy.

Although huge progress has been achieved in the downregulation of miR-21 in cancer cells, there are still many challenges to be resolved. More research is required to find the best strategy for downregulation of miR-21 and also the most feasible approach for delivery of this system into the tumor cells, especially *in vivo*. Until now, no clinical trials have been defined for the manipulation of miR-21 to reverse chemotherapy resistance. It is obvious that miR-21 is involved in many pathways and targets many genes, which are not all discovered yet, and it is important for the physiological function of the cells, but still, it is not clear whether complete knockout of miR-21 is safe for normal cells, or what is the long-term effect of miR-21 knockout on cancer cells. Furthermore, it is not clear for which stage of cancer and in which type of tumors, the knockout or knockdown method would be the correct option. Further research is required to find the missing pieces of this puzzle and hopefully, make use of this knowledge in the clinic to reduce drug resistance in cancer patients.

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Tara Akhtarkhavari: Writing – original draft. **Ahmad Reza Bahrami:** Writing – review & editing. **Maryam M. Matin:** Conceptualization, Writing-review & editing.

Declaration of competing interest

The authors have declared that no competing interest exists.

Data availability

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