REVIEW

Regulation of multidrug resistance by microRNAs in anti-cancer therapy

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Abstract   Multidrug resistance (MDR) remains a major clinical obstacle to successful cancer treatment. Although diverse mechanisms of MDR have been well elucidated, such as dysregulation of drugs transporters, defects of apoptosis and autophagy machinery, alterations of drug metabolism and drug targets, disrupti on of redox homeostasis, the exact mechanisms of MDR in a specific cancer patient and the cross-talk among these different mechanisms and how they are regulated are poorly understood. MicroRNAs (miRNAs) are a new class of small noncoding RNAs that could control the global activity of the cell by post-transcriptionally regulating a large variety of target genes and proteins expression. Accumulating evidence shows that miRNAs play a key regulatory role in MDR through modulating various drug resistant mechanisms mentioned above, thereby holding much promise for developing novel and more effective individualized therapies for cancer treatment. This review summarizes the various MDR mechanisms and mainly focuses on the role of miRNAs in regulating MDR in cancer treatment.

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1. Introduction

Although the use of chemotherapeutic agents has substantially improved the anti-tumor efficacy during the last decades, the development of multidrug resistance (MDR) remains the largest obstacle to the success of cancer chemotherapies. MDR is defined as the resistance of cancer cells to a diverse panel of structurally and functionally unassociated drugs[1]. This resistance can occur naturally (inherent resistance) or acquired during the course of chemotherapy or upon recurrence after successful chemotherapy[2,3].

The development of MDR is a complicated and multifactorial process. During the last few decades, diverse mechanisms have been implicated in the development of both intrinsic and acquired MDR. The main mechanisms include: (1) Overexpression of MDR transporters; (2) Defects in the apoptotic machinery; (3) Induction of autophagy; (4) Alteration of drug metabolism; (5) Alteration in drug targets and DNA repair; and (6) Disruption of redox homeostasis. However, the exact mechanisms of MDR in a specific cancer patient and the specific biomarker to define it, the cross-talk among these different mechanisms and how they are regulated are largely unknown.

Recently, numerous studies have demonstrated that microRNAs (miRNAs) play key regulatory roles in MDR through modulating many of the biological processes mentioned above. Therefore, miRNAs could be potential biomarkers and (or) targets for circumventing MDR in cancer chemotherapy. This review summarizes the various MDR mechanisms and focuses on the roles of miRNAs in regulating MDR in cancer treatment.

2. Mechanisms of multidrug resistance

2.1. Overexpression of MDR transporters

Overexpression of MDR transporters is one of the most important causes of chemoresistance[4,5]. The ABC transporter family members are the most widely studied MDR transporters[6,7]. These ABC transporter proteins have similar trans-membrane domains that can pump the chemotherapeutic drugs out of cancer cells against a concentration gradient in an ATP energy-dependent manner, thus reducing intracellular accumulation of chemotherapeutic agents, and protecting cancer cells from toxicity. To date, 48 ABC transporters have been detected in the human body[8], among which the most extensively characterized MDR transporters include P-glycoprotein (P-gp/ABCB1), multidrug resistance associated protein-1 (MRP1/ABCC1), and breast cancer resistant proteins (BCRP/ABCG2)[9-11].

The overexpression of ABCB1 has been shown to be associated with a large variety of chemotherapeutic drugs including anthracyclines, epipodophyllotoxins, vinca alkaloids, and taxanes[4,7,12,13]. Overexpression of the ABCC1 transporter also confers resistance to a wide range of anticancer drugs, such as anthracyclines, vinca alkaloids, epipodophyllotoxins, camptothecins, methotrexate, and mitoxantrone[12,14,15]. The substrates of ABCG2 include tyrosine kinase inhibitors (TKIs), anthracyclines, camptothecin-derived topoiso-merase I inhibitors, methotrexate and flavopiridols[16,17] (Fig. 1).

2.2. Defects in cell-cycle and the apoptotic machinery

After DNA damage is induced by anti-cancer drugs, the injured cancer cells can react in two ways: either by cell cycle arrest and damage repair, or by apoptosis and cell death if the DNA damage is too extensive to repair. The tumor suppressor protein (P53) plays a vital role during this process[18]. The effect of P53 on drug resistance has been studied extensively. Mutant P53, which often causes the loss of P53 function and MDR has been reported in many cancers including acute lymphoblastic leukemia, melanoma, osteosarcoma, breast, ovarian, and testicular cancers[19-21].

Apoptosis is the major type of cell death triggered by chemotherapy drugs. There are two established pathways of apoptosis: the intrinsic mitochondrial pathway and the extrinsic transmembrane pathway. The intrinsic pathway is mainly under the control of the BCL-2 family, which includes both pro-apoptotic proteins (BAX, BAK, BID, BIM,

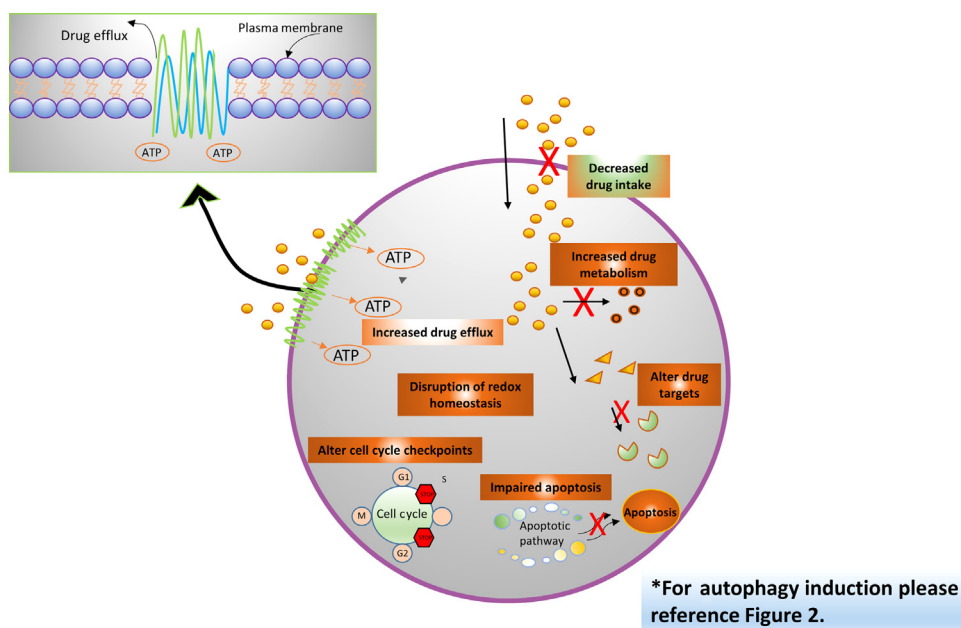**Figure 1**   The mechanisms underlying the development of multidrug resistance in cancers. Anti-drug resistance can occur at many levels, including dysregulation of drugs transporters which might lead to increased drug efflux and (or) decreased drug intake, defects in cell cycle and the apoptotic machinery, induction of autophagy (see Fig. 2), alteration of drug metabolism and target, as well as disruption of redox homeostasis.
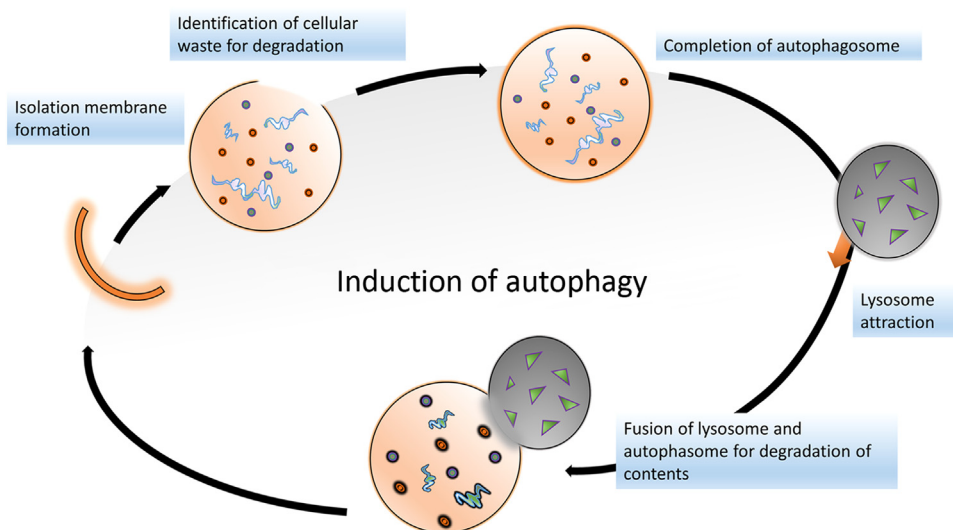
Figure 2 Key phases involved in the process of autophagy. Cellular stress such as chemotherapy can activate the autophagy pathway through several phases, including induction (formation of a pre-autophagosomal structure leading to an isolation membrane), vesicle nucleation (capturing and delivering cytoplasmic material to lysosomes for digestion), elongation/completion (elongating of the lipid membrane to enclose the target cargo, and completing the formation of an autophagosome), docking/fusing with the lysosome (forming a mature autolysosome), and cargo degradation (undergoing hydrolysis to degrade the vesicle's contents and completing macroautophagy).

BAD, and PUMA) and anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1)[22], whereas the extrinsic pathway is regulated mainly by "death receptors" of the tumor necrosis factor (TNF) receptor family. Various anti-cancer drugs, such as antimetabolites, DNA cross-linking and intercalating agents, alkylating agents, topoisomerase I/II inhibitors and TKIs, have been reported to induce the intrinsic or/and the extrinsic apoptotic responses in tumor cells, resulting in caspsase activation[23]. Defects in these apoptotic machineries have been described to play an important role in cancer cell drug resistance[24]. Cancer cells can escape apoptosis either by overexpression of anti-apoptotic proteins or under-expression of pro-apoptotic proteins. Anti-apoptotic protein BCL-2 overexpression is the most common mechanism of apoptosis evasion, which has been reported be involved in the resistance of cells in a variety of drugs, including doxorubicin, paclitaxel, etoposide, camptothecin, mitoxantrone and cisplatin[25-27]. Several other factors, including aberrant activation of protein kinase B, nuclear factor kappa B (NF-κB), phosphatase and tensin homolog (PTEN) have also been demonstrated to play an important role in developing drug resistance in various cancer types through interfering apoptosis machinery[28-30] (Fig. 1).

2.3. Induction of autophagy

Autophagy is a relative new mechanism of anti-cancer drugs resistance reported in many recent studies. It is an evolutionarily conserved catabolic process characterized by cellular self-digestion and the removal of excessive, long-lived or dysfunctional organelles and proteins *via* endosome and lysosome fusion, which results in the formation of autophagosomes[31] (Fig. 2). Three main subsets of autophagy with different cellular functions and means by which targets are delivered to lysosomes have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy. Among the three forms, macroautophagy is the most commonly studied[32].

Autophagy can occur as a physiological process in normal cells to eliminate damaged organelles and recycle macromolecules, thus assuring cellular homeostasis and protecting against cancer. In established tumor cells, autophagy can serve as a means of temporary survival in response to metabolic stress, such as anticancer drugs, that might mediate resistance to anticancer therapies. On the other hand, once the cellular stress is continuous and evolves to progressive autophagy, cell death ensues. This kind of autophagic cell death is a form of physiological cell death which is contradictory to type I programmed cell death (apoptosis). The double sided functions of autophagy implicate its paradoxical roles in anticancer treatments, increasing or diminishing their anticancer activity. However, an increasing amount of evidence suggests that autophagy's pro-survival function plays a significant role in chemoresistance in a many different cancer types[33-38].

Chemotherapeutic drugs can induce both apoptosis and autophagy. Autophagy helps cancer cells evade apoptosis and therefore contributes to chemoresistance. For example, in response to 5-fluorouracil (5-FU) and cisplatin, chemosensitive cell lines exhibited apoptosis, whereas chemoresistant populations exhibited autophagy. Generally, cancer cells that respond to drugs by inducing autophagy are more drug-resistant[39]. Therefore, targeting autophagy would probably be a promising therapeutic strategy to overcome antidrug resistance[37].

A number of molecular mechanisms have been shown to be implicated in autophagy-mediated chemoresistance. These include the EGFR signaling pathway[40], the aberrant expression of phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway[41], vascular endothelial growth factor (VEGF)[42], mitogen activated protein kinase 14 (MAPK14)/p38a signaling[43,44], as well as the tumor-suppressor gene P53 pathway[43].

2.4. Alternation of anti-cancer drug metabolism

Cancer cells can acquire resistance to a specific drug by altering drug metabolism. The super family of cytochrome P450 (CYP) enzymes play a critical role in this process.
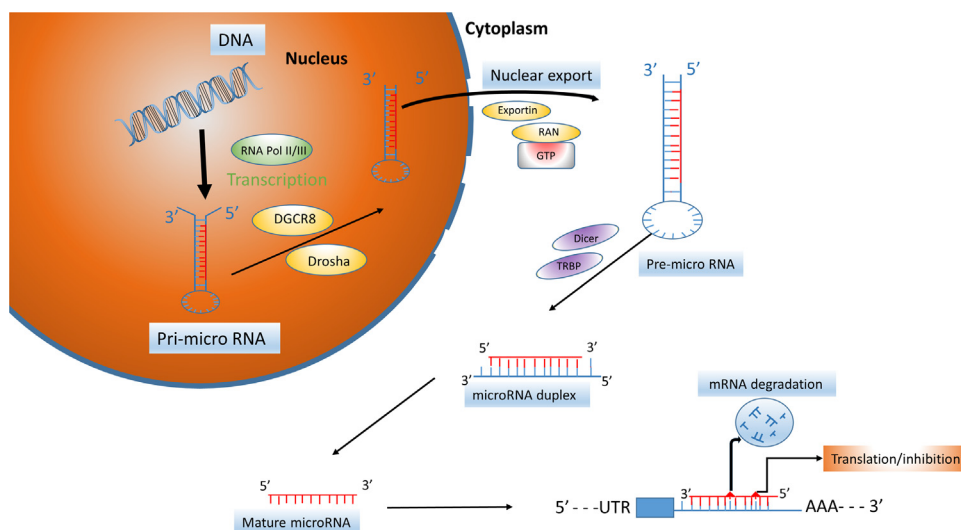
Figure 3 Biogenesis of microRNA and their functions. RNA polymerase II/III transcribes miRNA gene and generates a long primary transcript (pri-miRNA) ranging from 100 to 1000 nucleotides in length. The pri-miRNA consists of a hairpin stem, a terminal loop, and two single-stranded regions upstream and one downstream of the stem. The pri-miRNA is then processed by a RNase III endonuclease called Drosha into the precursor miRNA (pre-miRNA) which contains a hairpin structure of close to 70 nucleotides. The precise site of miRNA cleavage is determined by the DiGeorge Critical Region gene 8 protein (DGCR8) which forms a complex with Drosha. Pre-miRNA then leaves the nucleus by means of Exportin-5, a Ran-GTP dependant cytoplasmic transporter which can recognize a two-nucleotide overhang at the 3′ end of the RNA, and transports it to the cytoplasm. In the cytoplasm, the RNA is further processed by a second RNase III endonuclease, Dicer, into a miRNA:miRNA/duplex of approximately 19–24 nucleotides in length. One strand is selected to function as a mature miRNA and loaded into the RNA-induced silencing complex (RISC). Whereas the other miRNA/strand is degraded. The mature miRNA leads to translational repression or target mRNA.

The CYP enzymes are most expressed in human liver, intestine, and kidney. These enzymes are involved in the metabolism of a variety of chemotherapy drugs, including taxanes[45,46], vinblastine[45,46], vincristine[46], doxorubicin[46], etoposide[46], irinotecan[47], cyclophosphamide[48], ifosphamide[48]. Many factors, such as genetic polymorphisms, alterations in physiological conditions, disease status, intake of certain drugs or foods, or smoking can affect CYP activities. Such changes can alter pharmacokinetic profiles, and therefore the efficacy or toxicity of anticancer drugs. Genetic polymorphisms in CYPs sometimes result in reduced enzyme activity causing low metabolic clearance of drugs or low production of active metabolites[46]. The well-known example is the influence of CYP2D6 polymorphism on tamoxifen efficacy through the formation of endoxifen, which is an active metabolite of tamoxifen[49] (Fig. 1).

2.5. Alteration in drug targets and DNA repair

Chemoresistance can be caused by either quantitative or qualitative alterations of the drug targets. For example, expression levels of thymidylate synthase (TS), a key enzyme and target of 5-FU, and dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in metabolism of 5-FU, can predict 5-FU sensitivity[50]. Another example is ribonucleotide reductase subunit 2 (RRM2) which is an important cellular target of gemcitabine, plays an important role in gemcitabine resistance[51].

DNA topoisomerase II (Top II) is an essential nuclear enzyme that plays a critical role in DNA replication. Chemotherapy drugs, such as doxorubicin, idarubicin, mitoxantrone and etoposide, exert their anticancer function by targeting DNA-Topo II complexes, thereby leading to the DNA breakage and cancer cells death. Topo II–induced resistance to these drugs has been documented in many studies[52-54].

Enhanced DNA damage repair efficiency also plays a role in the development of MDR in cancer cells. This is specifically evident in the case of platinum agents and alkylating compounds, which exert their action *via* directly damaging of DNA[55]. There are three fundamental pathways to repair damaged DNA: nuclear excision repair (NER), base excision repair (BER) and DNA mismatch repair (MMR). Dysregulation of theses repair systems may be involved in chemoresistance[56] (Fig. 3). For example, hereditary nonpolyposis colorectal cancer (HNPCC) is strongly associated with specific mutations in the MMR pathway, which have been associated with reduced or absent benefit from 5-FU adjuvant chemotherapy[57]. Since these MMR alterations reduce the incorporation of the 5-FU metabolites into DNA, they decrease 5-FU-induced G2/M arrest apoptosis of cancer cells. In contrast, BRCA1/2 mutated breast and ovarian cancer, which exhibit homologous recombination–mediated repair deficiency, show increased sensitive to DNA-damaging chemotherapy drugs, such as platinum (Fig. 1).

2.6. Disruption of redox homeostasis

Disruption of redox homeostasis is another important resistance mechanism of anti-cancer drugs. Normal cells are capable of maintaining a balance between cellular oxidants and antioxidants, which is called redox homeostasis; whereas cancer cells usually exhibit higher levels of reactive oxygen species (ROS), which can

promote tumor progression and development. However, extremely high ROS will lead to cancer cell death. A variety of drugs exert their anti-cancer function (at least partly) through increasing ROS production, such as cisplatin[58], alkylating agents (Adriamycin and temozolomide)[59,60] and paclitaxel[61]. Nonetheless, some tumor cells can overcome drug-induced oxidative stress by enhancing their antioxidant systems, including heme oxygenase 1 (HMOX1), superoxide dismutase 1 (SOD1) and glutathione (GSH)[62]. Therefore, a new redox balance at a higher level of ROS accumulation and stronger antioxidant systems is established, which is called 'Redox Resetting'. Redox resetting has been shown to be implicated in drug resistance by interfering with other mechanisms, including elevated drug efflux, dysregulated apoptosis and autophagy, and altered drug metabolism drug targets[63].

Among antioxidant systems, GSH is the widely antioxidant agent reported to be involved in anti-cancer drugs resistance. Increased levels of GSH lead to chemotherapeutic drug resistance in numerous cancers[64]. GSH-dependent enzymes also have been implicated in MDR of cancer cells. One example is γ-glutamyltransferase (GGT), a key enzyme of GSH metabolism, which is able to sustain the 'GSH cycling' and maintain a high intracellular GSH level by metabolizing extracellular GSH and continuously supplying cysteine for the intracellular GSH re-synthesis. High GGT expression and/or increased GGT activity results in increased resistance to a number of anti-cancer drugs[65]. Another enzyme is glutathione *S*-transferases (GST) which can catalyze the conjugation of glutathione to chemical toxins. GST functions as the major detoxification mechanism in human body that can suppress oxidative stress and maintain normal cellular redox homeostasis. Many studies have shown that GST is relevant to the development of resistance to chemotherapy agents in different cancers[66-69]. Many drug-resistant cancers express high levels of GST. GST polymorphisms may affect drug metabolism and influence chemotherapy and cancer survival[70-72]. Some novel anticancer agents targeting GSTs are in development both in preclinical and clinical stages[73,74].

3.   miRNAs

miRNAs are a family of small single-stranded non-coding RNAs of 20–25 nucleotide length that are broadly conserved across species. Most miRNA loci are found in non-coding intronic transcription regions, but some are located in exonic regions[75]. Therefore, miRNAs do not encode any proteins. The main function of miRNA is regulating protein-coding gene expression post-transcriptionally by directly base pairing between the 5′ seed region of a miRNA and the 3′ untranslated region (3′UTR) of multiple target messenger RNA (mRNA), resulting in translational repression or mRNA degradation and lacking the ability to encode proteins[75]. It is of note that miRNA is not always associated with inhibitory or down regulatory effects. In rare circumstances, dependent on cell cycle and co-factors, miRNA can activate mRNA translation, thus up regulating protein levels[76].

The first miRNA molecule was identified in 1993 by Lee and collaborators[77]. To date, around 2600 unique mature human miRNAs have been discovered and there are certainly more to come (miRBase version 20)[78]. miRNAs have been shown to have vast effects on gene translation. More than 50% of all human gene translation is regulated by miRNA. Moreover, each miRNA can regulate numerous target genes, and, *vice versa*, the same target gene can be regulated by several types of miRNAs, creating a complex network[79-81]. The inherent complexity of this regulatory system allows miRNAs to control the global activity of the cell, including cell differentiation, proliferation, stress response, metabolism, cell cycle, apoptosis, and angiogenesis. Therefore, miRNAs may be involved in a broad range of human diseases, including cancer[82].

Deregulated miRNAs may cause up- or down-regulation of the miRNAs of interest, thus affecting the function of multiple target mRNAs, altering the expression of multiple proteins that are involved in cancer development, metastasis, angiogenesis and drug resistance[83-86]. miRNAs have also been shown to be potential biomarkers for early diagnosis and prognosis prediction in various cancers[86]. The present review summarizes the current knowledge on the role of miRNAs in anticancer drugs resistance.

4.   Aberrant expression of miRNAs and cancer drug resistance

Different miRNA expression profiles between cancerous cells and paired normal tissues from the same organ and cancer types have been documented in a number of recent studies[87,88]. Furthermore, significant changes in miRNA expression profiles were observed in drug-resistant cancer cells in comparison with parental drug-sensitive cancer cells[89]. The dysregulation of miRNAs expression profiles in cancer cells can lead to anti-cancer drugs resistance by abnormally modulating the expression of genes involved MDR mechanisms of action, such as ABC transporters genes, apoptosis and autophagy relates genes, drug metabolism genes, and redox systems related genes. These miRNAs could regulate MDR through targeting a specific gene or cellular signaling pathway, or simultaneously targeting several genes or cellular signaling pathways. Evidence pointing to the role of miRNAs in determining drug sensitivity and MDR is emerging[90,91]. Below, we focus on the MDR regulatory role of miRNA stratified by different MDR mechanisms.

4.1.   miRNAs regulate MDR transporters

4.1.1.   ABCB1/MDR1
Numerous studies have shown that miRNAs can modulate chemotherapy drug resistance through regulating the expression of ABC membrane transporters. P-gp, one of the most important MDR transporters, is responsible for the resistance to a large range of chemotherapy drugs. Overexpression of P-gp results from activation of the *ABCB1/MDR1* gene. Our laboratory demonstrated for the first time that both miR-451 and miR-27a were up-regulated in MDR cancer cell lines and caused a high level of P-gp[92]. Similar results were observed by Li et al.[93] in drug-resistant ovarian cancer cells. In contrast, other studies showed conflicting results. Kocalchuk et al.[94] reported the negative regulating role of miR-451 on P-gp expression in resistance of the MCF-7 breast cancer cells. Subsequently, similar phenomena were observed separately both in leukemia and hepatocellular carcinoma cell lines[95,96], suggesting the cell lines and environment may regulate miRNA functions.

A number of other miRNAs have been found to have a MDR modulation role by regulation ABCB1 expression. Zhao et al.[97] reported that up-regulation of miR-138 could significantly down-

regulate the expression of P-gp and reverse adriamycin resistance on the MDR leukemia (HL-60/VCR) cell line. Bao et al.[98] found that miR-298 could decrease P-gp expression in a dose-dependent manner by directing bound to P-gp 3′UTR and reverse doxorubicinresistance in breast cancer cells. miR-381 and miR-495 were also shown to be inversely associated with the expression of the *MDR1* gene and development of MDR[99]. Yang et al.[100] reported that miR-223 could down-regulate ABCB1 at both mRNA and protein levels and increase the HCC cell sensitivity to anti-cancer drugs. Other ABCB1-modulating miRNAs reported include miR-9[101], miR-122[102], miR-873[103].

Recently, high-throughput functional screening was used to identify additional MDR-related miRNAs. One miRNA found by this method is miR-508-5p. Overexpression of miR-508-5p was sufficient to reverse gastric cancer cell resistance to multiple chemotherapeutics *in vitro* and sensitize tumors to chemotherapy *in vivo*[104]. The most recent update study showed gastric cancer cells with up-regulated both miR-27b and miR-508-5p were more sensitive to chemotherapy. The two miRNAs have synergic effect and can form the miR-27b/CCNG1/P53/miR-508-5p axis which plays an important role in GC-associated MDR[105] (Table 1).

4.1.2. ABCG2/BCRP

ABCG2/BCRP is the first MDR transporter reported to be regulated by miRNA[106]. To date, several miRNAs have been identified to regulate ABCG2 expression. Overexpression of miR-328 down-regulated BCRP in breast cancer cells, thus increasing their sensitivity to mitoxantrone[107,108]. Other miRNAs showed similarly negative regulatory role on ABCG2 expression, including miR-519, miR-520(h), miR-212, MiR-181a, and MiR-487a[109-112].

4.1.3. ABCC1/MRP1

ABCC1/MRP1 is up-regulated in VP-16-resistant breast cancer cells (MCF-7/VP). Two miRNAs are reported to down-regulate ABCC1 expression and to reverse ABCC1-related MDR. Liang et al.[113] found MiR-326 was significantly down-regulated in a MCF-7/VP cell line compared to its parental cell line, while upregulating miR-326 level in the mimics-transfected VP-16-resistant cell line could down-regulate MRP-1 expression and sensitize these cells to VP-16 and doxorubicin. Pan et al.[114] found hsa-miR-1291 could directly down-regulate ABCC1 expression and sensitize the cancer cells to doxorubicin.

miRNAs could also regulate MDR by targeting other members of the ABC transporter family. For example, miR-23a enhances 5-FU resistance in microsatellite instability (MSI) CRC cells through targeting ABCF1[115]. miR-let-7g/i (let-7g/i) inhibits ABCC10 expression and enhances cellular sensitivity to DDP in human esophageal carcinoma (EC) cell lines[116].

Sometimes miRNAs exert their MDR modulating function by directly targeting several MDR related proteins at the same time. For example, over-expressed miR-129-5p can reverse chemoresistance by simultaneously targeting three members of ABC transporters (ABCB1, ABCC5 and ABCG1)[117]. Down-regulating miR-106a reversed MDR in human glioma cells by decreasing the expression of P-gp, MDR1, MRP1, as well as the expression of other apoptosis, survival, and inflammatory related proteins[118].

4.2. miRNAs regulate cell cycle and the apoptotic machinery

The tumor suppressor protein P53 is a critical mediator of cell cycle and apoptosis in response to different chemotherapeutic drugs. Several miRNAs are involved in the regulation of P53. Iida et al.[119] reported that upregulating miR-125b could suppress P53-dependent apoptosis and induce chemoresistance to doxorubicine, vincristine, etoposide and mafosfamide in Ewing sarcoma/primitive neuroectodermal tumor (EWS) cells. Liang and colleagues[120] demonstrated that overexpression of miR-140 could interfere with the growth and invasion of pancreatic duct adenocarcinoma cells by directly targeting inhibitor of apoptosis-stimulating protein of P53 (iASPP). MiR-122/cyclin G1 interaction was demonstrated to positively regulated P53 protein stability and transcriptional activity and affected doxorubicin sensitivity of human hepatocarcinoma cells[121]. On the other hand, the P53 protein itself could regulate certain miRNAs to induce cell cycle arrest and apoptosis. MiR-34a is one of P53 effector genes. The expression of miR-34a shows a strong linear correlation with wild-type P53 expression[122]. Overexpression of miR-34a can inhibit cell growth, induce apoptosis by targeting cyclin-dependent kinase 6 (CDK6)[123].

Several recent studies have showed that introduction of synthetic miR-34a mimics was able to induce cell death in P53-mutated medulloblastoma and glioblastoma cell lines[124]. "Restoration of P53/miR-34a regulatory axis decreases survival advantage and ensures BAX-dependent apoptosis of non-small cell lung carcinoma cells"[125].

BCL-2 is the most important anti-apoptosis protein. Quite a number of miRNAs have been shown to modulate MDR by targeting BCL-2. Xia and colleagues[126] found that in MDR gastric cancer cells significant downregulation of miR-15b and miR-16 was concurrent with the upregulation of BCL-2 protein expression, whereas upregulation of miR-15b or miR-16 dramatically reduced BCL-2 protein level and sensitized the cells to anti-cancer drugs. Another study by Cittelly et al.[127] found that downregulation of miR-15a/16 mediated BCL-2 activation and promoted tamoxifen resistance in breast cancer. Dong et al.'s study[128] found that miR-21 was involved in gemcitabine resistance by directly upregulating BCL-2 expression in pancreatic cancer cells. Other miRNAs found to directly target BCL-2 using Western blot and luciferase activity assays include miR-497[129], miR-200bc/429 cluster[130], miR-1915[131], miR-214[132] miR-195[133], and miR-205[134].

Furthermore, miRNAs can exert the apoptosis-regulating function by target other members of BCL-2 family proteins. For example, the anti-apoptotic protein BCL-XL can be modulated by miR-574-3p[135]. miRNA-101 can directly targeting MCL-1 and sensitizes hepatocellular carcinoma cells to doxorubicin-induced apoptosis[136]. On the other hand, miRNAs could also target some pro-apoptotic BCL-2 family proteins to modulate apoptosis. For instance, miR-494 could induce TNF-related apoptosis-inducing ligand (TRAIL) resistance in non-small cell lung cancer (NSCLC) through the down-modulation of BIM[137]. Up-regulation of miR-365 can induce gemcitabine resistance by directly down-regulating apoptosis-promoting protein BAX expression[138].

In addition, several miRNAs have been shown to regulate extrinsic apoptotic pathways. Quintavalle and colleague[139] reported that increased levels of miR-30 b/c and miR-21 in TRAIL resistant glioma cells could impair TRAIL dependent

apoptosis by inhibiting the expression of caspase-3 and TAp63. Up-regulation of miR-21 could promote the resistance of nasopharyngeal carcinoma cells to cisplatin by suppressing the pro-apoptotic factors programmed cell death 4 (PDCD4) and FAS ligand (FAS-L)[140].

PTEN is another important tumor suppressor gene correlated to chemotherapeutic response. Different miRNAs have been shown to regulate tumor cell chemoresistance by targeting PTEN and/or its downstream kinase, including miR-21[141,142], miR-22[143], miR-221[144], miR-214[145], miR-19a/b[146], miRNA-17-5p[147] and miR-222[148] (Table 1).

4.3.   miRNAs regulate autophagy

Induction of autophagy is another important mechanism of anti-cancer drug resistance which can be modulated by miRNAs. The entire process of autophagy, including autophagic induction, vesicle nucleation, vesicle elongation and completion can be modulated by different miRNAs. Our laboratory first reported the regulatory role of miRNAs on autophagy in 2009[149]. Since then, a growing body of evidence indicates that miRNAs can regulate autophagy related genes to modulate anti-cancer drug resistance. However, the precise roles of miRNAs in the autophagy pathways have not yet been well elucidated.

miR-30a is the first microRNAs reported by our group to suppress stress-induced autophagy through inhibition of beclin 1 expression149. Beclin is an essential protein in autophagy. miR-30a can inhibit autophagy via suppression of beclin 1 and ATG5 (another key autophagy promoting protein). Thus, upregulation of miR-30a can sensitize chronic myelogenous leukemia (CML) cells to imatinib treatment. Targeting miR-30a promotes autophagy in response to imatinib treatment and enhances imatinib activity against CML[150,151]. Dysregulation of "miRNA-30a activating beclin-1 related autophagy" is also found to be contributed to chemoresistance of osteosarcoma cells[152], as well as resistance to sorafenib in renal cell carcinoma cells[153].

miR-30d is another member of the miR-30 family identified by our group which acts similarly to miR-30a in regulating autophagy. miR-30d can directly target the binding sequences in the 3′UTR of beclin 1, affecting the expression of this key autophagy-promoting protein. Moreover, we found that inhibition of the beclin 1–mediated autophagy by the miR-30d mimics sensitized anaplastic thyroid carcinoma cells to cisplatin both in vitro (cell culture) and in vivo (animal xenograft model)[154].

It is noticeable that both autophagy and apoptosis function in cell growth, survival, development, and death. Therefore, these two pathways might have cross-talk, and be regulated by the same miRNA. For example, miR-204 shows both an anti-apoptosis effect and autophagy inhibitory effect[155,156]. Up or down regulation of miR-204 may change the transition of apoptosis and autophagy; subsequently, influence chemosensitivity. The most recent study showed that combined overexpression of miR-16 and miR-17 can suppress the expression of beclin 1 and Bcl-2, and, in turn, inhibit autophagy and promote apoptosis. Thus, upregulation of miR-16 and miR-17 can dramatically sensitize paclitaxel-resistant lung cancer cells to paclitaxel treatment[157]. There are still a number of miRNAs reported to regulate anti-cancer drugs sensitivity by targeting autophagy. Examples include miR-155 mediated drug resistance in osteosarcoma cells via induction of autophagy[158], miR-200b regulated autophagy associated with chemoresistance in human lung adenocarcinoma[159]. In addition, miR-15a and miR-16 induced autophagy and enhanced chemo-sensitivity of camptothecin[160], and miR-181a suppressed autophagy and sensitized gastric cancer cells to cisplatin[161] (Table 1).

4.4.   miRNAs control anti-cancer drug metabolism

miRNAs may regulate the superfamily of P450 (CYP) metabolic enzymes, thereby modulating patterns of drug metabolism, including those of anti-cancer drugs. Accumulating evidence suggests that miRNAs may modulate MDA through regulation of CYP enzymes. For example, miR-27b may negatively regulate CYP1B1, a key member of the CYP family mediating metabolism of a wide range of drugs. Decreased expression of miR-27b and the subsequent high expression of CYP1B1 could be one of causes for resistance to docetaxel in cancerous cells[162,163]. The most recent studies showed that miR-27b can also sensitize cancer cells to a broad spectrum of anti-cancer drugs in vitro and in vivo by activating P53-dependent apoptosis and reducing CYP1B1-mediated drug detoxification[164]. Other CYPs are also reported to be modulated by miRNA. For instance, CYP1A1 can be targeted by miR-892a[165], CYP2J2 is inhibited by let-7b[166], and CYP3A4 is downregulated by miR-148a[167] (Table 1).

4.5.   miRNAs modulate drug targets and DNA repair

miRNAs seem to impact anti-cancer drugs sensitivity by modulating the expression of drug targets. For example, miR-192 and miR-215 may influence 5-FU sensitivity by targeting TS enzyme in colorectal cancer cells[168]. Furthermore miR-27a, miR-27b, miR-134, and miR-582-5p are able to post-transcriptionally regulate DPD protein expression, which is also involved in sensitivity to 5-FU–based chemotherapy[169]. miR-211 can reduce the expression of RRM2, the important cellular target of gemcitabine, and increase the sensitivity of pancreatic cancer cells to gemcitabine[170]. miRNA let-7 was also found to negatively regulate RRM2 expression and sensitize PDAC cells to gemcitabine[171].

Several studies have demonstrated that miRNAs can influence the chemosensitivity of cancer cells through interfering with DNA-repair pathways in cancer cells. Valeri and collaborators[172] showed that in colorectal cancer cells, overexpression of miR-21 dramatically downregulated the expression of MMR proteins (hMSH2 and hMSH6) and reduced the therapeutic efficacy of 5-FU. MMR proteins, MSH2, MSH6 and MLH1-PMS2, were also reported to be negatively regulated by miR-155[173]. In breast cancer cell lines, miR-182 was able to downregulate BRCA1 protein expression, impair homologous recombination–mediated repair, thereby increasing cellular sensitivity to poly (ADP-ribose) polymerase (PARP) 1 inhibitor[174]. Sun et al's study[175] showed that miR-9 could downregulate BRCA1 and impede DNA damage repair in ovarian cancer, subsequently increasing the sensitivity of cancer cells to cisplatin and PARP inhibitors (Table 1).

Table 1 Roles of miRNA on regulation of drug resistance in Cancers.

MiRNA function	miR(s)	Target of miR(s)	Effect(s)	Ref.
Regulation of MDR transporters	miR-451	ABCB1/MDR1	Downregulates P-gp in cancer cells	94–96
	miR-27a miR-451	ABCB1/MDR1	Upregulate P-gp in MDR cancer cells	92,93
	miR-138	ABCB1/MDR1	Down regulates P-gp and reverses adriamycin resistance on the MDR cell line in leukemia.	97
	miR-298	ABCB1/MDR1	Decreases P-gp expression and reverse doxorubicin resistance in breast cancer cells	98
	miR-381 miR-495	ABCB1/MDR1	Negatively regulate *MDR1* gene	99
	miR-223	ABCB1/MDR1	Down-regulates ABCB1 mRNA and protein levels and increases the HCC cell sensitivity to anti-cancer drugs	100
	miR-9 miR-122 miR-122 miR-508-5p	ABCB1/MDR1	Mediate MDR in cancer cells by targeting ABCB1.	101–105
	miR-328	ABCG2/BCRP	Down-regulates BCRP and increases the sensitivity to mitoxantrone in breast cancer cells	107,108
	miR-519 miR-520(h) miR-212 miR-181a miR-487a	ABCG2/BCRP	Negatively regulate ABCG2 expression	109–112
	miR-326	ABCC1/MRP1	Down-regulates MRP-1 expression and sensitizes cancer cells to VP-16 and doxorubicin	113
	Hsa-MiR-1291	ABCC1/MRP1	Down-regulates ABCC1 expression and sensitizes cells to doxorubicin.	114
	miR-125b miR-140	P53	Suppress p53-dependent apoptosis and induce chemoresistance	119,120
	miR-122	P53	Increases p53 protein stability and contribute to chemosensitivity.	121
	miR-34a	CDK6	Induces apoptosis and inhibits cell growth	123
	miR-15b miR-16 miR-21	BCL2	Upregulate of BCL-2 protein expression	126–128
	miR-497 miR-200bc/429 miR-1915 miR-214 miR-195 miR-205	BCL2	Directly target BCL-2	129–134
	miR-574-3p	BCL-XL	Modulates the anti-apoptotic protein BCL-XL	135
	miR-101	MCL-1	Sensitizes hepatocellular carcinoma cells to doxorubicin-induced apoptosis	136
	miR-494	BIM	Down-regulates the BIM	137
	miR-365	BAX	Down-regulates BAX expression and induces gemcitabine resistance	138
	miR-30 b/c miR-21	Caspase-3 PDCD4	Impair TRAIL dependent apoptosis	140
	miR-21 miR-22 miR-221 miR-214 miR-19a/b miRNA-17-5p miR-222	PTEN	Target PTEN and/or its downstream kinase	141–148
Induction of autophagy	miR-30a	Beclin 1 and *ATG5*	Activates beclin 1–related autophagy and confers anti-cancer drugs resistance	149–153
	miR-30d	Beclin	Inhibits beclin 1–mediated autophagy	154
	miR-155 miR-15a miR-16	—	Induce autophagy and enhance chemosensitivity	158,160
	miR-200b miR-181a	*ATG12* *ATG5*	Suppress autophagy	159,161
Modulation anti-cancer drug metabolism	miR-27b	CYP1B1	Negatively regulates CYP1B1 expression	162,163
	miR-892a	CYP1A1	Sensitizes cancer cells to a broad spectrum of anticancer drugs.	165
	let-7b	CYP2J2	—	166

Table 1 (*continued*)

MiRNA function	miR(s)	Target of miR(s)	Effect(s)	Ref.
	miR-148a	CYP3A4	Downregulates the expression of CYP3A4.	167
Modulation of drug targets	miR-192 miR-215	TS enzyme	Influences 5-Fu sensitivity	168
	miR-27a miR-27b miR-134 miR-582-5p	DPD enzyme	Modulate the sensitivity of 5-Fu–based based chemotherapy	169
	miR-211 let-7	RRM2	Regulate RRM2 expression and sensitize PDAC cells to gemcitabine	170,171
	miR-21	MMR proteins	Downregulates hMSH2, hMSH6 expression and reduces 5-Fu sensitivity	172
	miR-155	MMR proteins	Negatively regulates MSH2, MSH6 and MLH1-PMS2 expression	173
	miR-182 miR-9	BRCA1	Down-regulate BRCA1 expression and increased the sensitivity of cancer cells to cisplatin and PARP inhibitors	174,175
Regulation GSH and GSH-depended enzymes	miRNA-27a	GSH	Modulates GSH biosynthesis	178
	miR-513a-3p	GST	Negatively regulates *GSTP1* gene expression	179
	miR-133b	GST	Reduces GST expression, and inverses chemotherapy resistance	180

—Not known.

ATG12, autophagy-associated gene 12; *ATG5*, autophagy-associated gene 5; CDK6, cyclin-dependent kinase 6; DDP, dihydropyrimidine dehydrogenase; GSH, glutathione; GST, glutathione *S*-transferases; MDR, multidrug resistance; MMR, mismatch repair; PDCD4, pro-apoptotic factors programmed cell death 4; PTEN, phosphatase and tensin homolog; RRM2, ribonucleotide reductase subunit 2; TS, thymidylate synthase.

4.6. *miRNAs regulate GSH and GSH-depended enzymes*

Several recent studies have shown the regulatory role of miRNA on redox systems[176,177]. However, such a role in the field of cancer MDR has not been fully studied. One report found that miRNA-27a contributed to cisplatin resistance through modulation of GSH biosynthesis[178]. Several other studies demonstrated that miRNA was able to target GST mediated drug metabolism to regulate MDR. Zhang et al.[179] reported that miRNA-513a-3p could negatively regulate *GSTP1* gene expression. Overexpression of miR-513a-3p resensitized cisplatin-resistant A549 cells to cisplatin[179]. Another study found that increased miR-133b expression could reduce GST-π expression, and reverse chemotherapy drug resistance[180].

4.7. *Master miRNAs modulate multiple targets*

The most recent studies have suggested the existence of master miRNAs which could target multiple essential drug resistance pathways, therefore, are capable of improving the sensitivity to a broad spectrum of anticancer drugs. For example, miR-1271 can regulate cisplatin resistance of human gastric cancer cell lines by targeting IGF1R, IRS1, mTOR, and BCL-2[181]. miRNA-127 reversed adriamycin resistance *via* modulating ABC transporters MDR1 and MRP1, apoptosis related proteins (RUNX2, P53, BCL-2, survivin), as well as the AKT signal pathway[182]. miR-214 behaved as a key hub by coordinating fundamental signaling networks, such as PTEN/AKT, β-catenin, and tyrosine kinase receptor pathways, and also regulated the levels of crucial gene expression modulators, such as epigenetic repressor EZH2, P53, transcription factors TFAP2, and another miRNA

(miR-148b)[183]. Discovery of more master miRNAs may be a powerful tool to overcome MDR.

5. Conclusions

MDR in cancer treatment is a highly complex process encompassing many different mechanisms. miRNAs, due to their extensive gene regulatory roles, are able to regulate nearly all the mechanisms of MDR. Therefore, miRNA, especially the master miRNAs, could be ideal biomarkers to predict chemotherapeutic response, as well as potential targets to overcome MDR in the future.

Acknowledgments

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