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# microRNAs in cancer chemoresistance: The sword and the shield

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ABSTRACT

Cancer is a multifactorial disease and one of the leading causes of mortality worldwide. Cancer cells develop multiple strategies to reduce drug sensitivity and eventually lead to chemoresistance. Chemoresistance is initiated either by intrinsic factors or due to the prolonged use of chemotherapeutics as acquired resistance. Further, chemoresistance is also one of the major reasons behind tumor recurrence and metastasis. Therefore, overcoming chemoresistance is one of the primary challenges in cancer therapy. Several mechanisms are involved in chemoresistance. Among them, the key role of ABC transporters and tumor microenvironment have been well studied. Recently, microRNAs (miRNAs) regulation in tumor development, metastasis, and chemotherapy has got wider interest due to its role in regulating genes involved in cancer progression and therapy. Noncoding RNAs, including miRNAs, have been associated with the regulation of tumor-suppressor and tumor-promoter genes. Further, miRNA can also be used as a reliable diagnostic and prognostic marker to predict the stage and types of cancer. Recent evidences have revealed that miRNAs regulation also influences the function of drug transporters and the tumor microenvironment, which affects chemosensitivity to cancer cells. Therefore, miRNAs can be a promising target to reverse back chemosensitivity in cancer cells. This review comprehensively discusses the mechanisms involved in cancer chemoresistance and its regulation by miRNAs.

## 1. Introduction

Cancer is one of the major non-communicable diseases and the leading cause of death worldwide. Chemotherapy is the most commonly preferred therapeutic approach because of its effectiveness and widespread availability. However, most of the chemotherapies cause adverse side effects, and the long-time use induces chemoresistance. Chemoresistance is a mechanism when the prolonged use of an anticancer agent or a group of anticancer agents fails to show its anti-cancerous property towards cancer cells and allows cancer cells or tumors to grow and metastasize into other organs aggressively. Chemoresistance is mainly of two types such as innate-chemoresistance and acquired-chemoresistance [1]. Majorly, three factors are involved in drug resistance: first, decreased intake of the drugs inside the cell or increased release of drugs outside of the cell. The second is the degradation and deactivation of intracellular thiols, and the third is the advanced intracellular DNA repair mechanism. Besides these, several factors including, mutation, hypoxia, cancer stem cells, and epigenetic changes, are involved in the regulation of chemoresistance [2,3]. Among them, noncoding RNAs (ncRNAs), one of the basic epigenetic modifications, play a crucial role in chemoresistance.

ncRNAs are endogenous, single-stranded RNAs that can modulate the expression of receptors and genes involved in cancer chemoresistance. ncRNAs are also known as epigenetic modifiers, as they regulate gene expression by modifying local chromatin statuses or by non-chromatin status such as by DNA methylation [4]. According to transcript size, ncRNAs are classified into two categories - small ncRNAs (~22 nucleotides in size) and long ncRNAs (lncRNAs, 200 nucleotides to >100 kb in size). microRNA (miRNA) is the most active small ncRNAs compared to other small ncRNAs and plays a significant role as 'the sword and the shield' in the chemoresistance mechanism [5]. This review comprehensively discusses the emerging role of miRNAs in altering the chemosensitivity and the mechanism involved in chemoresistance.

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## 2. Mechanisms behind chemoresistance in cancer

### 2.1. Multi-drug resistance (MDR)

MDR is one of the significant causes of chemoresistance. MDR is a phenotype of the resistance for cancer cells, where a particular drug or variety of drugs have shown no effect towards cancer cells, though they are different in structure as well as different in mode of action. MDR-associated pathways are the most common pathway by which cancer chemotherapeutics stay remain unproductive as anticancer agents. MDR is mediated by a multifactorial mechanism where at least two to three resistance mechanisms are going simultaneously. The most common mechanisms involved in MDR are increased drug detoxification, increased drug repair mechanism, variation in intracellular drug concentration, modulation of the cell cycle, and altered influx as well as the efflux of chemotherapeutics. MDR occurs mainly by two ATP-binding cassettes (ABC) superfamily of transport proteins, the first is P-glycoprotein mediated, and the second is Non-P-glycoprotein intervened [6].

#### 2.1.1. P-glycoprotein (P-gp)-mediated drug resistance

Humans have two membrane transporter proteins, such as MDR1 and MDR2. The *MDR1*-encoded P-gp is a membrane-associated glycoprotein whose primary function is to efflux out toxins, drugs, or anticancer agents from the cells. P-gp is responsible for the resistance of some drugs such as platinum agents, taxanes, anthracyclines, alkaloids, and topoisomerase inhibitors [7]. The overexpression of this protein represents the inherent chemoresistance property of cancer cells. For example, adherent chemoresistant SCLC and NSCLC cell lines have shown the aberrant expression of *MDR1*. In addition, *MDR1* expression is low in clinical samples of both lung cancer as well as normal lung tissues. Therefore, P-gp may play a minor role in different cancer chemoresistance [8]. Platinum agents are the major therapeutics used in cancer treatment. It has been reported that a significant percentage of resistance to the platinum agents occurs by reducing influx and amplifying efflux through P-gp in ovarian cancer cells. Active efflux via P-gp has played a great role in the resistance of camptothecin analogs, which is inhibiting DNA replication by obstructing Topoisomerase I activity [9–11].

#### 2.1.2. Non P-glycoprotein (Non-P-gp) drug resistance mechanism

Another important member of the ABC superfamily is *MRD-associated protein 1 (MRP1)* encoded non-P-glycoprotein. Similar to the P-gp, *MRP1* is also an integral membrane phosphoglycoprotein, involved in MDR. In contrast to P-gp, *MRP1* requires cofactors, glutathione (GSH), glucuronic acid, or sulfate in the drug-efflux mechanism [7]. Some cell lines have shown drug resistance without overexpression of P-gp, which points out the role of *MRP1* in their chemoresistance mechanism. In addition to *MRP1,* some more members of the ABC-transporters family, such as breast cancer resistance protein (BCRP) and lung-resistance-related- protein (LRP), play an essential role in cancer chemoresistance. BCRP is mainly involved in the resistance of camptothecin analogs and topo I inhibitors, which have a significant role in lung cancer chemotherapy. The expression of LRP correlates with resistance to doxorubicin. Chemoresistant-cancer patients usually have higher expression of ABC-transporters, which indirectly represents the higher quantity of drug efflux from cells [12].

### 2.2. Enzymes involved in drug resistance

Some enzymes play a key role in reducing the effect of the drug inside the cells and making cells resistant to that drug. The major enzymes involved in drug resistance are glutathione-dependent enzymes, topoisomerases, thymidylate synthase, cytochrome P450 enzymes etc. Among the stress-releasing enzymes, glutathione-dependent enzymes such as glutathione-related enzymes glutathione S-transferase (GST) and glutathione peroxidase (GPx) reduce the cytotoxicity effect of anticancer agents inside the cell through GPx by utilizing GSH to remove reactive oxygen intermediates [9]. GST-π isoenzyme is also highly expressed in lung tumors of smokers compared to non-smokers. Alterations in the GST correlate with the development of drug resistance in lung tumors. In addition to the P-gp and non-p-gp-mediated MDR, alteration in topoisomerase II (topo II) activity leads to MDR. An elevated level of topo II is allied with resistance to certain DNA-damaging agents (platinum-based agents). The lower levels of topo II expression may predict to reduce the sensitivity of human lung cancer to several drugs such as cisplatin, doxorubicin [9]. Thymidylate synthase (TS) plays a crucial role in DNA biosynthesis and is the target of many chemotherapeutic agents. Tumor cells resistant to cisplatin and doxorubicin have shown an elevated level of TS. The cytochrome P450 superfamily is also involved in many drug-metabolizing reactions [9].

### 2.3. Drug influx, metabolism, and efflux

The equilibrium between the influx and efflux of a drug is essential inside the cancer cell. Drugs come in a cell in different ways, from diffusion to endocytosis or through a transporter. Declining the drug concentration within the cells causes ineffective chemotherapeutics. Various factors are involved in lowering the drug concentration, such as decreasing the absorption, decreasing the number of transporters, and mutation in the drug transporters. For example, cells resistant to methotrexate have commonly mutated folate binding proteins [13]. Another important reason for the decline of intracellular drug concentration is ABC-transporters mediated signaling cascade, as depicted in Fig. 1. Tumor cells can acquire resistance to a specific drug by altering pathways involved in drug metabolism. Some metabolic enzymes superfamily of cytochrome p450 (CYP) enzymes, CYP3A4, play a significant role in chemoresistance [14].

### 2.4. Gene expression

The expression of genes involved in tumor progression and therapy plays a major role in response to chemotherapeutics. The expression of *breast cancer susceptibility gene 1* (*BRAC1)* is one of the predictive markers of cisplatin-based chemotherapy in many cancers. Patients with the overexpression of *BRCA1* have a lower survival rate because of poor prognosis. For example, docetaxel-received patients have shown higher expression of *BRAC1* whereas, combinatorial chemotherapy of gemcitabine and cisplatin have shown the lower expression of *BRAC1* [15]. Lower BRCA1 expression might improve the response of cisplatin-based chemotherapy with cisplatin and paclitaxel in epithelial ovarian cancer (EOC) patients [16]. BRCA1 expression is also a marker of progression and overall survival in sporadic breast cancers treated with anthracycline-based chemotherapy [17]. Similar to BRAC1, DNA repair enzymes such as excision repair cross-complementation group 1 (ERCC1) are reported to have some connection with platinum-based therapy. Low ERCC1 expression levels are prognostic for response and advancement of free survival (PFS) among [10].

### 2.5. DNA damage and repair system

Apoptosis is one of the major mechanisms by which anticancer agents kill cancer cells by fragmenting their genetic materials. Apoptosis also occurs if the DNA repair system is not able to recover the extensive DNA damage. Alteration of transcription factors, genes involved in cell-death pathways, and variation in apoptotic signaling pathways are among the reasons for chemoresistance. Mutation in these genes, such as tumor suppressor, apoptotic markers *bcl-2, bcl-x* can cause drug resistance and prevent apoptosis.

All chemotherapeutics directly or indirectly target the genetic materials of the cancer cells. Damaged DNA induces apoptosis, reduces cell proliferation, genetic instability. There are some mechanisms involved in DNA repair mechanism. For example, platinum-based agents such as

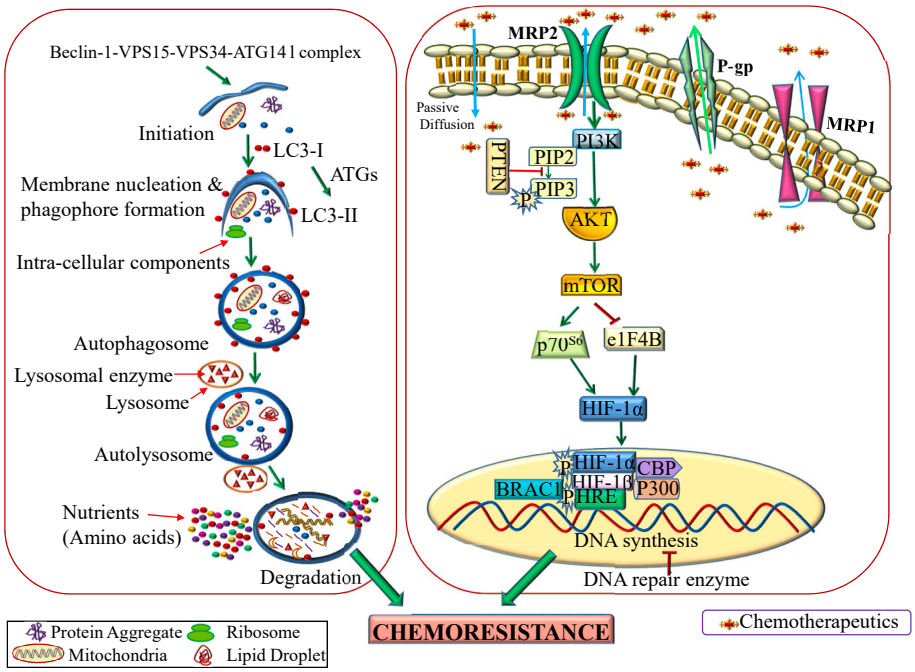


**Fig. 1. Role of autophagy and hypoxia in cancer chemoresistance.** Autophagy supports cancer cells to survive under stress conditions like hypoxia. In general, autophagy is initiated by forming phagophore, then specific proteins like ATGs and LC3 form autophagosome. At the final stage, the autophagosome merges with the lysosome to form an autolysosome and degrades drug molecules to avert cell death. The presence of the beclin-1-VPS15-VPS34-ATG14 l complex represents the initiation of autophagy. Hypoxia initiates PI3K signaling leading to AKT phosphorylation which activates HIF-1α and leads to chemoresistance. In general, chemotherapeutics (drugs) enter the cells by diffusion. The ABC-transporters (P-gp, MRP1, and MRP2) reduce the drug concentration by drug efflux and lead to chemoresistance.

cisplatin and carboplatin cause DNA damage, leading to the apoptosis of cancer cells. The resistance to these agents occurs by the DNA repair systems. There are mainly three basic pathways involved in the DNA damage repair system-Nuclear excision repair (NER), Base excision repair (BER), and DNA mismatch repair (MMR) [14]. These all pathways directly or indirectly contribute to chemoresistance. Another compensatory DNA damage response pathway may counterbalance an abnormal function of the DNA repair pathway. The expression of various DNA repair genes like *BARD1, SIRT1,* and *H2AFX* have been shown to be involved in chemoresistance. *BARD1* is interrelated with resistance to the platinum-binding agents [11]. Some enzymes involved in DNA repair mechanisms are also involved in chemoresistance. The most important two enzymes are ERCC1 and ribonucleotide reductase regulatory subunit M1 (RRM1). ERCC1 is a crucial enzyme involved in the NER-mechanism. ERCC1 is associated with resistance of platinum-based agents, whereas high expression of RRM1 is associated with cisplatin, docetaxel, and gemcitabine resistance [10,18].

### 2.6. Autophagy

The high density of cancer cells inside the solid tumor hinders blood flow, leading to insufficient nutrients and oxygen. Thereby, the effectiveness of therapeutic drugs also differs. In addition, the lessened blood flow produces a toxic environment by reducing the clearance of breakdown products within the tumor. Cancer cells adapt 'autophagy' to maintain cellular homeostasis by decreasing the supply of nutrients. Autophagy is a progressive preserved mechanism for degrading cellular damaged organelles and unfolded as well as aggregated proteins to maintain intracellular homeostasis. Autophagy, is also known as macroautophagy, plays a crucial role in chemoresistance. Autophagy is a self-protective mechanism where cells degrade drug molecules to prevent apoptosis, as depicted in Fig. 1. The microenvironment of cells plays a vital role in the autophagy mechanism. Autophagy is one of the mechanisms assists to escape from cell death in cellular stress or metabolic stress [19]. In the presence of cytotoxic agents such as cisplatin, and 5-fluorouracil (5-FU), chemoresistant cells have shown autophagy phenotype and a morphology reminiscent of type II programmed cell death. In contrast, chemosensitive cells have undergone apoptosis [11]. Similar to apoptosis, tumor suppressor gene p53 also plays a significant role in autophagy activation. Guo et al. showed that p53 contributes to the activation of autophagy to protect the cell from apoptosis under nutrient-deprived microenvironments [20].

### 2.7. Hypoxia condition

Reduced blood supply to cancer cells causes deprived supply of oxygen and lead to the hypoxic condition. Hypoxia is also involved in the mechanism of chemoresistance. Because many drugs cause genotoxicity by generating free radicals, the anticancer activity of these therapeutic drugs is reduced due to the lack of oxygen [21]. Solid tumors are more resistant to chemo- and radiotherapy because of insufficient vascularization due to the space and mass constraints. Therefore, cells of solid tumors can grow in hypoxia conditions. In hypoxia conditions, cells can alter the expression of genes involved in chemoresistance and endothelial cell growth by prompting one or more transcription factors such as hypoxia-inducible factor-1 (HIF-1) [11]. Doxorubicin and methotrexate-related resistance is occurred due to hypoxia. Doxorubicin-resistant lung tumors have shown lower expression of *VEGF,* which is mediated by hypoxia conditions [9].

### 2.8. Cancer stem cells

Cancer stem cells are the subpopulation of cells with the ability to self-renewal and differentiation. These cells are also involved in chemoresistance through various mechanisms, as depicted in Fig. 2. The expression of CD133 correlates with chemoresistance in small lung cancer (SCLC). Clinical samples have reported that $CD133^{+}$ stem cells present in SCLC are highly tumorigenic and positively associated with chemoresistance [22]. CSCs have advanced intrinsic resistance to chemotherapy than cancer cells because CSCs have the capability to inactivate the drug by amplified expression of detoxifying ALDH enzymes, improved DNA repair mechanism which prevents the action of platinum and alkylating agents, as well as shrink drug activation via quiescence, and enhanced drug efflux by the upregulation of the ABC transporters [13,23]. Irregular signaling embryonic pathways such as Notch Hedgehog (Hh) and Wnt/β-catenin of CSCs play a major role in chemoresistance. For example, $CD133^{+}$ glioblastoma stem cells have shown prominent resistance to paclitaxel, carboplatin, etoposide, and

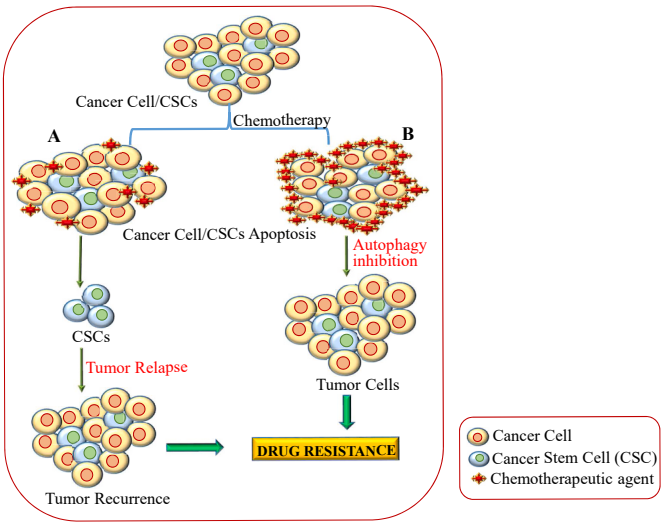


**Fig. 2. Role of cancer stem cells (CSCs) in chemoresistance.** The bulk of the tumor cell population contains cancer cells and CSCs. (A) Conventional chemotherapy targets both cells in the bulk of the tumor but selectively causes cell death to the limited proliferative cancer cells. CSCs acquire chemoresistance, and the presence of CSCs leads to tumor relapse, followed by tumor recurrence. (B) Autophagy alters the tumor microenvironment, which influences chemosensitivity. In addition, cancer cells degrade drug molecules to avert cell death in autophagy conditions. Hence, autophagy inhibits the apoptosis of both CSCs and cancer cells, thereby leading to drug resistance.

temozolomide by enhancing DNA repair mechanism through activating DNA damage checkpoint kinases and Wnt signaling cascade [24,25].

### 2.9. Epigenetic regulation

Epigenetic modifications such as DNA methylation, histone modifications, and regulation of ncRNA play a significant role in chemoresistance. In general, tumor suppressor genes are transcriptionally silenced by hypermethylation. In contrast, tumor-promoter genes such as *hTERT* are overexpressed by hypermethylation. Demethylation at the promoter region of *MDR1* promotes cancer cells to gain a multi-drug-resistant phenotype and reduces the intracellular accumulation of anticancer agents [26]. In contrast, promoter methylation of *BMP4* resensitizes gastric cancer cells to cisplatin by decreasing the expression of BMP4 [27]. Similarly, incubating with DNA methyltransferase inhibitors inhibits the expression and function of *ABCG2/BCRP* [28]. The inhibitors of DNA methylation such as 5-Aza-2′-deoxycytidine (decitabine; DAC) can enhance the efficacy of other drugs such as cisplatin and carboplatin to the tumor. Therefore, the combinatorial effect of epigenetic inhibitors and conventional chemotherapeutic agents might be more efficacious than the single agents [13]. In addition to DNA methylation, histone modification also plays a major role in chemoresistance [29]. In general, overexpression of EZH2, a member of histone lysine methyltransferases (KMTs) has been observed in drug-resistant cells compared to chemosensitive cancers cells. Overexpression of EZH2 initiates overall phosphorylation of kinases in serine and tyrosine residues, thereby leading to chemoresistance. However, the inhibition of EZH2 by KMTi inhibitor, EPZ011989, shown to reduce phosphorylation and activate tumor suppressors to reverse chemoresistance [30]. Recently, different combinations of KMTi have been shown to reverse back the chemoresistance of chemotherapeutics [31]. For example, 3-deazaneplanocin A, an EZH2 inhibitor, combined with panobinostat, a HDAC inhibitor, has been shown to reduce chemoresistance in chemoresistant glioblastoma cells [32]. Similar to DNA methylation and histone modification, ncRNAs, especially miRNAs, play a dynamic role in cancer chemoresistance [29].

## 3. Role of miRNA in cancer chemoresistance

miRNAs play a significant role in various biological processes such as cell cycle, cell proliferation, metastasis, and cell signaling pathways [33]. Dysregulation of miRNAs can cause aberration to different physiological functions. Alteration in the expression of miRNAs can improve or deteriorate the chemotherapeutic response. In addition, miRNAs regulate chemoresistance by altering the expression of tumor-suppressor genes, tumor-promoter genes, and oncogenes. miRNAs can reverse the chemosensitivity by limiting the gene expression involved in autophagy, cell survival, and DNA repair mechanisms, thereby altering cell survival, as depicted in Fig. 3. The downregulation of REV3-like DNA-directed polymerase zeta catalytic subunit (REV3L) or the upregulation of miR-29a inhibits the cell growth by arresting in the $G_2$/M phase when co-treated with cisplatin [34]. REV3L is responsible for translation DNA synthesis. DNA repair pathway is another mechanism involved in chemoresistance. Flap endonuclease 1 (FEN1) is involved in chemoresistance by regulating numerous factors involved in DNA repair pathways. Tumor suppressor miR-140 reduced the DNA repair mechanism by complementing FEN1 at 3′untranslated region3 (UTR). Therefore, upregulation of miR-140 reverses the chemosensitivity to breast cancer cells by targeting FEN1. In addition, transcription factor/repressor Ying Yang 1 (YY1) directly binds to the miR-140 promoter and triggers miR-140 expression, decreasing doxorubicin resistance [35].

miRNAs can regulate chemoresistance by altering the expression of different transcription factors associated with Epithelial-Mesenchymal Transition (EMT) [36,37]. Tumor suppressor miR-218 has an inverse correlation with 'master switch' runt-related transcription factor 2 (RUNX2), which controls several genes involved in the development of osteoblasts. The other function of RUNX2 is to modulate angiogenesis via cell proliferation, invasion, and angiogenesis. The overexpression of miR-218 increases cisplatin sensitivity by the downregulation of RUNX2 and enhances apoptosis and cell cycle arrest at the $G_0$/S phase in NSCLC [38]. miR-218 is also inversely correlated with EMT transcription factors such as Slug and ZEB2. The upregulation of miR-218 augments the chemosensitivity of cells to cisplatin as well as obstructs cell migration and invasion through suppression of Slug and ZEB2 expression by blocking the 3′-UTR regions of *Slug* and *ZEB2* [39]. miRNAs regulate various signaling pathways associated with chemoresistance mechanisms. For example, downregulation of miR-499a inhibits cell proliferation, induces cell cycle arrest, reduces colony formation, metastasis and enhances chemosensitivity to cervical cancer cells by targeting ex-determining region Y box 6. Therefore, inhibition of miR-499a could reverse the sensitivity of cisplatin in cervical cancer cells [40]. miRNAs have been involved in the regulation of various processes in chemoresistance as outlined below:

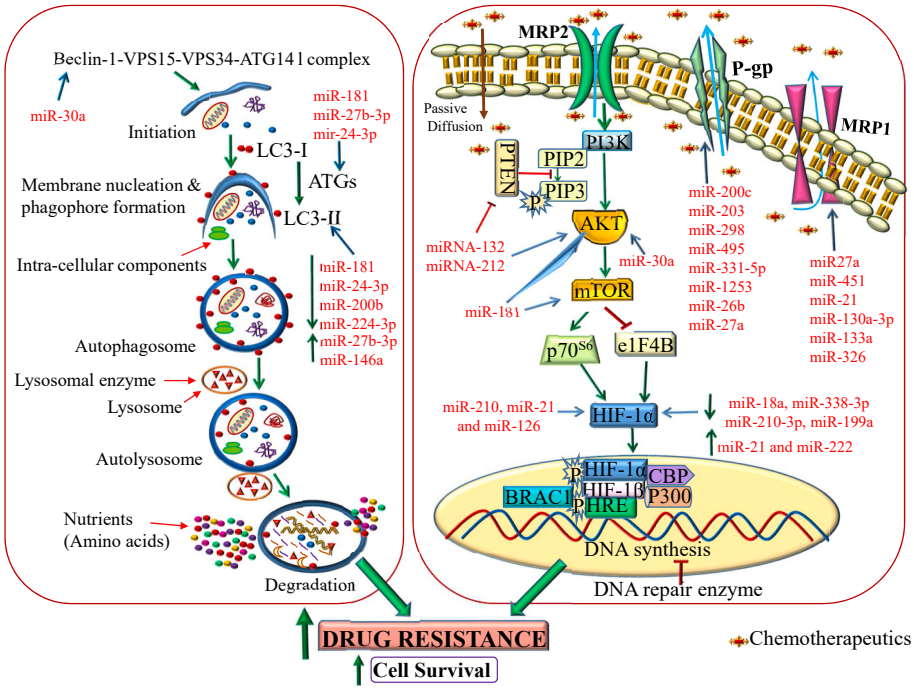


**Fig. 3. miRNA regulation in cancer chemoresistance.** miRNAs target the key factors involved in autophagy and hypoxia, thereby altering the chemoresistance. Simultaneously, miRNAs also regulate the chemosensitivity in cancer cells by targeting ABC-transporters.

### *3.1. miRNA regulates MDR proteins in chemoresistance*

In addition to several signaling pathways, the cell fate also depends on the regulation of different genes and transcription factors. Phosphatase and tensin homolog *(PTEN)* are negative regulators of the PI3K/AKT signaling pathway and function as tumor suppressor gene regulating cell cycle, apoptosis, and formation of many types of solid tumors. miRNA-132 and miRNA-212 also modulate NF-κB/PTEN-AKT cascade. Overexpression of miR-132/-212 represses the PTEN expression, which activates AKT phosphorylation and the NF-κB pathway and thereby enhances breast cancer resistance protein (BCRP) expression. BCRP is a member of *MRD-associated protein 1 (MRP1)* family, functions as a drug efflux transporter, and is directly associated with chemoresistance. Upregulation of miR-132/-212 leads to BCRP-based doxorubicin efflux in MCF-7 cells. Therefore, overexpression of miR-132/212 has been observed in doxorubicin-resistant breast cancer tumors and cells [41]. BCRP is another target of miR-328. Overexpression of miR-328 enhances mitoxantrone sensitivity by downregulating BCRP in breast cancer cells [42,43]. NF-κB is another target of miR-152, and it also regulates many apoptotic markers. Upregulation of miR-152 enhances cisplatin sensitivity in lung cancer A549/cis cells by downregulating anti-apoptotic proteins Bcl-2 and NF-κB [44]. Similar to MRP1, MRP4 is another member of the ABC transporter family involved in drug distribution and cell communication. This transporter protein is downregulated by miR-124-3p and miR-4524-5p at the protein level but not

mRNA level in hepatocellular carcinoma. However, downregulation of MRP4-related proliferation and multiple drug resistance can be alter through both miRNA. On the other side, circHIPK3 functions as a competitive endogenous RNA which sponging miR-124-3p and miR-4524-5p, thereby restores MRP4 expression [45].

#### *3.1.1. ATP-binding cassette sub-family C member 1 (ABCC1)*

Tumor suppressor miRNAs can modulate ABC-transporters, which modulate MDR in cancer cells. For example, miR-27b, miR-508-5p, miR-129-5p, and miR-107 can impede the expression of a certain family member of ABC-transporters, thereby enhancing the sensitivity of 5-FU to gastric cancer cells [46–49]. ABCC1 is target of some miRNAs like miR-133a and miR-326. These miRNAs have been shown to enhance the sensitivity of doxorubicin in HCC cells by modulating ABCC1 [55]. miR-326 also enhances doxorubicin and etoposide sensitivity to breast cancer cells by downregulating ABCC1 [56]. Similarly, MRP1 or ABCC1, P-gp, and lung-resistance protein (LRP) are downregulated by miR-146a and enhance cisplatin sensitivity [39]. In addition, cisplatin sensitivity increased by enhanced cell cycle arrest, apoptosis, and repressed cell viability, invasion, migration through upregulation of cleaved caspase-3 and targeting cyclin J [39]. MRP1 is also regulated by miR-21 in cisplatin resistance. miR-21 plays in multiple ways in cisplatin resistance. Among them, three mechanisms are important. First, miR-21 induces drug efflux by increasing the expression of MDR1 and MPR1. Second, miR-21 prevents oxidative damage and inhibits cisplatin-regulated apoptosis by enhancing the level of cystathionine, GSH, SOD, and GST-π expressions and thereby promoting the drug inactivation. The last one, miR-21 is also regulating different cell signaling pathways. It is reported here that miR-21 increases cisplatin resistance by activating the PI3K/AKT signaling pathway and triggers transcription factors such as E2F-1 and Twist [57]. Similarly, miR-21 considerably inhibits the paclitaxel-induced apoptosis by altering P-gp expression [58]. Another study has shown that miR-1291 directly represses ABCC1 expression, which increases sensitization of doxorubicin to cancer cells [59].

#### *3.1.2. ATP-binding cassette sub-family C member 2 (ABCC2)*

ABCC2 is a member of ABC-transporters, which efflux various molecules across extra- and intra-cellular membranes and make the cells more resistant to drugs. Cisplatin-resistant cells have shown higher expression of ABCC2 and Bcl-xL and lower expression of Let-7c. Therefore, Let-7c regulates the sensitivity of DDP in A549/DDP resistant cells by targetting ABCC2 and Bcl-xL [50]. By bioinformatics analysis, Zhan et al. have also hypothesized that oncogene *c-MYC* and other genes like *STAT3, cyclin D1* are target points for let-7c. The higher expression of these genes causes cisplatin resistance in NSCLC [50]. *ABCC2* mRNA has been identified as a target of miR-379 by RNA interference in CRC cells. Transfection of miR-297 enhances the sensitivity of vincristine (HCT-8/VCR) or oxaliplatin (HCT-116/L-OHP) to

respective CRC resistant cells by targeting ABCC2 [51]. Similar to ABCC2, different miRNAs can regulate the expression of other members of the ABC-transporter superfamily like ABCA1, ABCC1, ABCC5, ABCC10, and ABCE1 in the HCC patient samples and clinically overcome the resistance [52]. ABCC5 is also another target of miR-148 and miR-128. In breast cancer cells, miR-148 and miR-128 reverse back the effect of doxorubicin to induce cell death by impeding the expression of BMI1 and ABCC5 [53,54].

#### 3.1.3. ATP-binding cassette sub-family B (MDR/TAP) member 1 (ABCB1)

ABCB1/P-glycoprotein or P-gp, MDR1 is one of the important protein among ABC-transporter, function as efflux pump. P-gp has an inverse correlation with miR-200c and miR-203 in the doxorubicin-resistant breast cancer cell line. More than 50 fold-lower expressions of miR-203 and miR-200c have been observed in the KCR (doxorubicin-resistant cell line) compared to the parental wild-type MCF-7, whereas 100,000-fold higher expression of ABCB1 has been observed in KCR cells compared to MCF-7 cells. Therefore, the expression of miR-203 and miR-200c reverses back the sensitivity of doxorubicin in KCR by altering the activity of the ABCB1 efflux pump [60]. Transfection of miRNAs has been shown to modify the sensitivity of drugs in breast cancer cells. For example, transfection of miR-298 and miR-1253 enhance the doxorubicin sensitization in breast cancer cells by downregulating the expression of P-gp [61]. Similar to miR-203 and miR-200c, miR-26b has an inverse correlation with P-gp in colorectal cancer cells. In 5-FU resistant cells, P-gp is overexpressed as miR-26b is downregulated, due to the hypermethylation to CpG islands of *miR-26b* promoter site, which induced the expression of P-gp. However, overexpression of *miR-26b* increased 5-FU in 5-FU resistant CRC cells by downregulating P-gp [62]. Another miR-27a also enhances the 5-FU effect in HCC cells by suppressing MDR1/P-gp and β-catenin expression [63]. P-gp is another target of miR-107, which enhances the oxaliplatin by impeding the expression of P-gp, cyclin D1, and c-myc [49]. In contrast, miR-27a enhances oxaliplatin resistance by inducing MDR1/P-gp, lung resistance protein (LRP), and Bcl-2 expression in gastric cancer [64]. Transfection of miR-331-5p and miR-27a improve the effect of doxorubicin in K562 chronic myelogenous leukemia cells by downregulating P-gp expression [65]. In gastric cancer, ABCB1 is also another target of miR-495, which sensitizes the resistant gastric cells to paclitaxel by altering ABCB1 expression [66].

#### 3.1.4. ATP-binding cassette sub-family B (MDR/TAP) member 9 (ABCB9)

ABCB9, another member of the ABCB family, is a target of miR-24, which functions as a reliable biomarker to predict the efficacy of the drug. miR-24 reverses the paclitaxel sensitivity in breast cancer cells by modulating ABCB9 [67]. In another study, miR-31 regulates cisplatin resistance by modulating the ABCB9, a transporter associated with antigen processing-like (TAPL), which is involved in drug cellular trafficking and chemotherapy-related MDR [68]. The overexpression of miR-31 suppresses DDP-induced apoptosis by targeting ABCB9 in NSCLC cell lines. They also mentioned that overexpression of miR27a and miR-451 bring extensive MDR to cancer cells by modulating the expression of MDR1/P-glycoprotein [68]. miRNAs could also modulate the MDR by targeting other members of the ABC transporter family. For example, miR-23a increases 5-FU resistance in microsatellite instability (MSI) CRC cells through targeting ABCF1115. In contrast, miR-let-7g/i (let-7g/i) improves DDP sensitivity in human esophageal carcinoma (EC) cell lines by suppressing the ABCC10 expression [69].

Similar to miRNA, lncRNA also regulates the expression of these MDR-related proteins, including MDR1 and multidrug resistance proteins (MRPs). MALAT1, an oncogenic and highly conserved nuclear lncRNA involved in tumor development, radiosensitivity and chemosensitivity of tumor cells. MALAT1 reduced DDP sensitivity *in vitro* and *in vivo* by upregulating MRP1 and MDR1 via triggering STAT3. Fang et al., found that A549/MALAT1 cells were significantly resistant to DDP-induced apoptosis, while A549/DDP/shMALAT1 cells had a high apoptosis rate induced by DDP [70]. The overexpression of lncRNA X-Inactive Specific Transcript (XIST) relates to cisplatin resistance in NSCLC by downregulating miR-144-3p, as miR-144-3p is a target of XIST. Knockdown of XIST suppresses cell proliferation, and migration promotes cell apoptosis and diminishes the expression of MDR1 and MRP1 in A549/DDP and H460/DDP cells [71].

Similar to miRNA, lncRNA also takes part in the regulation of drug transporters such as ABC transporter. Antisense noncoding RNA in the INK4 locus (ANRIL), oncogenic lncRNA, is previously popular for its epigenetic regulation on its neighboring gene cluster p15/CDKN2B-p16/CDKN2A-p14/ARF and cancer progression. ANRIL is also involved in cisplatin resistance by regulating drug transporters, including MRP1 and ABCC2 in lung cancer [72]. Another oncogenic lncRNA colon cancer-associated transcript-1 (CCAT1) and transcription factor sex-determining region Y-box 4 (SOX4) regulate miR-130a-3p in cisplatin-resistant NSCLC cells. SOX4 is a transcription factor regulator involved in embryonic development. CCAT1 and SOX4 negatively interact with miR-130a-3p and contribute to DDP resistance in NSCLC by downregulating miR-130a-3p expression. Knockdown of SOX4 increases the sensitivity of cisplatin to DDP resistant NSCLC cells and decreases ABCG2 expression [73]. ABCG2 is also another target of miR-212/328, thereby MiR-212/328 reversed back imatinib sensitivity in CML cells [43,74].

### 3.2. miRNA regulates hypoxia in chemoresistance

One of the common characteristics of the TME is hypoxia, which aids in tumor dormancy, making the cells aggressive and resistant against chemotherapeutic drugs. Hypoxia is mediated by hypoxia-inducible factor-1 (HIF-1), which is regulated by many transcription factors. The aberrant expression of these TFs and/or HIF-1 leads to the formation of a hypoxic and chemoresistant TME [75]. In addition, hypoxia-induced high expression of signal transducer and activator of transcription 3 (STAT-3) contributed to cancer stemness and chemoresistance [76]. Also, increased expression of TGF-β2 was found to increase cancer stemness and increased expression of HIF-1α aided in GLI2 induced chemoresistance in colorectal cancer cells [77,78]. Overexpression of HIF-2α increased cancer stemness and cMyc expression, which caused paclitaxel resistance by activating Wnt and Notch pathways in breast cancer cells [78]. In a study, Sabry et al. identified miR-210, miR-21, and miR-126, whose aberrant expression impacted the HIF-1α-VEGF signaling pathway in CRC [79]. High expression of HIF1α was observed to cause an increase in the miR-421 expression, which further inhibited E-cadherin (EMT biomarker) and caspase-3 (apoptosis regulator), enhancing cisplatin resistance in Gastric cancer [80]. Cisplatin sensitivity also increased in cisplatin-resistant oral squamous cell carcinoma cells (OSCC) by miR-132. Tumor suppressor miR-132 inhibiting the proliferation, invasion, and enhanced the pro-apoptotic ability of cisplatin in OSCC via regulating TGF-β1/Smad2/3 signals [81]. Another miR-141-3p can restore the trastuzumab sensitivity in breast cancer cells repressing CDK8 which alter phosphorylation level of SMAD2/SMAD3 via TGF-β [82]. Therefore, TGF-β is one of the epicenteric factor, involved in chemoresistance, can be targeted by many miRNA to regain the chemosensitivity. Downregulation of miR-18a, miR-338-3p, and miR-199a and upregulation of miR-21 was observed to cause chemoresistance by enhancing HIF-1α expression in cancer cell lines [83–86].

Overexpression of miR-222 was found to inhibit VHL, a protein that forms part of the VHL E3 ubiquitin ligase complex, which helps in the ubiquitination and degradation of unwanted proteins. Inhibition of VHL was correlated with increased HIF-1α stability, further increasing vincristine resistance in retinoblastoma cells [87]. Moreover, hypoxia was found to induce EMT and increase 5-FU resistance in p53 (tumor suppressor) mutant or deficient CRC via downregulation of miR-34a. Downregulated miR-34a increased Inh3 expression, a regulatory subunit for PP1 that helps to regulate STAT3, thereby promoting EMT-mediated cellular metastasis [88]. In another study, hypoxia

promoted cell cycle arrest in the G1 phase and inhibited apoptosis. It was further found that miR-210-3p regulated HIF-1α and HIF-2α in a negative feedback loop where high expression of HIF-1α promoted miR-210-3p, but knockdown of HIF-1α reduced miR-210-3p expression, which increased HIF-2α expression. Additionally, simultaneous knockdown of HIF-1α and HIF-2α increased temozolomide sensitivity in glioblastoma cells [89]. Similarly, HIF-1α-mediated repression of miR-338-5p enhances chemoresistance in CRC by activating STAT3/Bcl2 through IL-6. IL-6 is the direct target of miR-338-5p, which activates STAT3/Bcl2 in hypoxia-mediated CRC drug resistance. Upregulation of miR-338-5p in CRC cells and PX-478, a HIF-1α inhibitor, can enhance the sensitivity of oxaliplatin (OXA) to CRC by repressing the HIF-1a/miR-338-5p/IL-6 feedback [90]. These results suggest that HIF-1α plays a significant role in the adaptation of malignant cells in the hypoxic environment contributing to tumor aggressiveness and resistance to chemotherapy. Hypoxia was found to induce autophagy via downregulating miR-224-3p expression, which is a direct target for ATG5, thereby increasing temozolomide resistance in glioblastoma and astrocytoma cells [91].

### 3.3. miRNA alters autophagy in chemoresistance

Autophagy, a process that helps cells achieve cellular homeostasis, is characterized by the formation of autophagosomes that envelop abnormal or irregular proteins, damaged organelles, or other cytoplasmic components under stress conditions. Finally, the fusion of the autophagosome and the lysosome forms autophagolysosome where the degradation of these unwanted components occurs, which provides amino acids and other nutrients for cell growth and metabolism [92]. Cancer cells achieve chemoresistance via autophagy by 1) inhibition of autophagic cell death and 2) activation of autophagy upon stress-induced by radiotherapy and chemotherapy, causing resistance to cancer treatments [93].

Dysregulation of various genes and ncRNAs involved in autophagy has been reported to contribute to chemoresistance in many cancers [94]. *PTEN* is a key regulator of autophagosome formation, which prevents the inhibitory effect of PI3K/PKB on autophagy, thereby triggering autophagy. However, activating the PI3K/AKT/mTOR signaling pathways inhibits cancer cell autophagy and stimulates cancer cell development [95]. The upregulation of miR-181 hinders cell growth and metastasis and prompts apoptosis and autophagy in A549/DDP cells through the PTEN/PI3K/AKT/mTOR pathway. In the same way, the downregulation of miR-181 repressed autophagy-associated proteins such as LC3 and ATG5 [95]. miR-181c leads to cisplatin resistance in NSCLC cells by targeting Wnt inhibition factor 1 [96]. Similarly, miR-27b-3p enhances oxaliplatin sensitivity in CRC patients by reducing the expression of c-Myc, which downregulates the expression of ATG10, a member of 36 autophagy (ATG) genes. In general, a lower level of miR-27b-3p has been observed in oxaliplatin-resistant cells compared to its parental cells, and at the same time, under oxaliplatin treatment, these resistant cells have shown a higher level of autophagy phenotype compared to parental cells. Overexpression of miR-27b-3p inhibits autophagy by impeding the LC3-I to LC3-II conversion, downregulating ATG10, and enhancing chemosensitivity by repressing c-Myc. Therefore, c-Myc/miR-27b-3p/ATG10 regulatory axis plays a key role in CRC chemoresistance [97].

Paclitaxel was demonstrated to induce high expression of Cdx1 that activated an autophagy-associated signaling pathway that was further observed to enhance resistance against paclitaxel-induced cytotoxicity in CSCs [98]. In addition, chemotherapy was observed to enhance Beclin-1 (positive regulator of autophagy) expression, which inhibited pAKT, further proposing autophagy-induced chemoresistance through inhibition of AKT pathway in neuroblastoma cell lines [99]. miR-30a expression was found to be downregulated in osteosarcoma cells resulting in enhanced Beclin-1 expression contributing to resistance against doxorubicin via activation of autophagy [100]. Higher expression of miR-25 was found to diminish ULK-1 expression that increased Beclin-1 and ABCG-2 (ABC-transporter), causing inhibition of autophagic cell death and drug resistance in breast cancer cells [101]. Further, miR-200b downregulation was found to directly increase ATG12 expression causing docetaxel resistance in human lung adenocarcinoma (ADL) cell lines [19].

miRNAs are not only regulating the sensitivity and chemoresistance involved in monotherapy. They are also engaged in double chemotherapy. Pan et al. have reported that the downregulation of miR-24-3p contributes to etoposide and cisplatin resistance by aiming autophagy associated gene 4A *(ATG4A)*. *ATG4A*, another member of 36 autophagy (ATG) genes, is primarily involved in mammalian cells' autophagy process. miR-24-3p has an inverse relation with ATG4A. Therefore, the downregulation of miR-24-3p increases etoposide and cisplatin resistance to small cell lung cancer (H446) by activating ATG4A [102]. Another transcriptor involved in apoptosis is CHOP (DNA damage-inducible transcript 3), which produces endoplasmic reticulum stress. CHOP and miR-146a have an inverse correlation, and miR-146a controls CHOP expression by targeting 3′ UTR region of *CHOP* in lung cancer cells. CHOP is directly connected to the modulation of autophagy or apoptosis-associated genes such as LC3-II, death receptor 5 (DR5), and telomere repeat-binding factor 3, respectively. The upregulation of CHOP raised the expression of LC3-II, DR5, and TRB3, whereas the downregulation of CHOP increased cisplatin resistance [103].

### 3.4. miRNAs enhance the sensitivity of chemotherapeutics by targeting CSCs

CSCs are critical for cancer therapy because, in general, standard chemotherapeutics target cancer cells but not CSCs. A study has shown the population of $CD44^{+}/CD24^{-/low}$ breast cancer stem cells (BCSC) remain the same in the tumor after docetaxel, doxorubicin, cyclophosphamide and trastuzumab chemotherapies [104]. Even the population of BCSC was amplified after 12 weeks of continuous chemotherapy [104]. One of the main reasons behind the chemoresistance nature of CSCs is the overexpression of ABC proteins. Interestingly, in the past few years, investigations have shown that miRNAs can affect the resistant nature of CSCs by altering the expression of ABC proteins. For example, miR-328 and miR-451 enhance the chemosensitivity in CSCs by targeting ABCG2 and ABC subfamily B member 1.

In addition, the expression level is different in normal cells, cancer cells, and CSCs. In general, CSCs are rich in onco-miRs compared to tumor-suppressive miRNAs. For example, tumor-suppressive miRs such as Let-7, miR-16, miR-20b, miR-107, and three clusters of miR-200 have shown low-level expression in BCSCs compared to breast cancer cells [105]. Similar to breast cells, lower expression of miR-34a, let-7b, miR-106a, and miR-141 have been observed in $CD44^{+}$, $CD133^{+}$, integrin $a2b1^{+}$ prostate CSCs and SP cells [106]. Therefore, altering the expression of these tumor-suppressive miRNAs may alter the chemosensitivity of the drugs. In general, miR-200c is expressed at a low level in pancreatic CSCs (PCSCs), but overexpression of miR-200c enhances the sensitivity of gemcitabine to PCSCs [107]. Similarly, overexpression of another tumor-suppressive miR-145 reduces self-renewal capacity and reverses back the chemosensitivity of 5-FU and cisplatin in gastric cancer cells by targeting CD44 directly [108]. Interestingly, higher expression of CD44 enhances the expression of ABCG2, which increases the chemoresistance and self-renewal property of cancer cells. However, further investigation revealed that miR-145 enhanced chemosensitivity by suppressing the expression of ABCG2 in gastric cancer cells [108].

CD44 is also the target of another tumor suppressor, miR-223, which is underexpressed in $CD44^{+}CD24^{-/low}$ triple-negative breast cancer stem cells compared with non-CSCs. Further extensive investigation revealed that miR-223 significantly improved the cytotoxicity of doxorubicin or cisplatin to MDA-MB-231-CSCs and MDA-MB-435-CSCs by targeting *hematopoietic cell-specific protein 1-associated protein X-1 (HAX-1)* [109]. Another side, they also have shown that miR-223 enhanced

chemosensitivity by inducing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) via downregulating *HAX-1* [109]. In breast cancer, overexpression of miR-16 declined the self-renewal abilities of BCSCs in mice and enhanced the sensitivity of doxorubicin to MCF-7 cells by targeting W1P1 [110]. Some miRNAs target proteins have been shown to be involved in apoptosis and enhance chemosensitivity. miR-125b enhanced the sensitivity of temozolomide in glioblastoma CSCs by targeting pro-apoptotic Bcl-2 antagonist killer 1 [111]. In contrast, overexpression of miR-5100 enhanced cisplatin resistance in lung CSCs by targeting Rab6, a small GTP-binding protein, belongs to the Ras superfamily, which is regarded as a pro-apoptotic factor [112].

miRNAs alter numerous stemness-associated signaling pathways to overcome chemoresistance; among them, the Notch signal is a key pathway. miR-136 increased paclitaxel sensitivity in ovarian cancer cells by repressing the Notch3 signaling pathway [113]. Similarly, miR-181b enhanced cisplatin sensitivity and reduced CSCs phenotype in lung cancer cells by targeting Notch signal [114]. Notch is also a direct target of miR-34a. Therefore, ectopic miR-34a expression enhanced doxorubicin sensitivity and repressed cancer stem cell properties in breast cancer cells by targeting the Notch1 [115].

## 4. Conclusion

Over the past few years, scientific research has developed therapeutic approaches to target several factors involved in tumor development and cancer progression. Among several factors, chemoresistance followed by tumor relapse is a major challenge in cancer treatment. Simultaneously, researchers found that miRNA can be used as a novel target for cancer treatment as it regulates DNA translational, mRNA and protein expression and reprograms several cellular signaling pathways. Hence, miRNAs would bring new hope for cancer therapy [116]. Recently, several comprehensive scientific research reveals that miRNA plays 'the sword and the shield' role in chemoresistance and tumor development [117]. miRNAs can enhance the chemosensitivity by weakening the self-renewal abilities of CSCs, repressing the function of the ABC transporter, and altering the tumor microenvironment [118]. Besides, miRNAs also enhance the apoptosis of cancer cells by targeting proteins involved in the cell cycle, metastasis, and signaling pathways. In addition, miRNA can also be used as a reliable diagnostic and prognostic marker to predict the stage and types of cancer [119,120]. Therefore, miRNA can be focused as a new therapeutic target to overcome chemoresistance, however, clinical correlation with advancement in miRNA-based diagnostic warrants future research and its therapeutic applications.

## Declaration of competing interest

The authors declare no conflict of interest.

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## References

[1] P. Magee, L. Shi, M. Garofalo, Role of microRNAs in chemoresistance, Ann. Transl. Med. 3 (2015), https://doi.org/10.3978/j.issn.2305-5839.2015.11.32.
[2] S. Shukla, D. Penta, P. Mondal, Breast Cancer Metastasis and Drug Resistance. Advances in Experimental Medicine and Biology, Adv Exp Med Biol., 2019, pp. 293–310.
[3] P. Mondal, J. Natesh, D. Penta, S.M. Meeran, Progress and promises of epigenetic drugs and epigenetic diets in cancer prevention and therapy: a clinical update, Semin. Cancer Biol. (2020), https://doi.org/10.1016/j.semcancer.2020.12.006.
[4] X. Deng, X. Song, L. Wei, C. Liu, X. Cao, Epigenetic regulation and epigenomic landscape in rice, Natl. Sci. Rev. 3 (2016), https://doi.org/10.1093/nsr/nww042.
[5] P. Mondal, J. Natesh, M.A. Kamal, S.M. Meeran, Non-coding RNAs in lung cancer chemoresistance, Curr. Drug Metabol. 20 (2020) 1023–1032, https://doi.org/10.2174/1389200221666200106105201.
[6] A.K. Larsen, A.E. Escargueil, A. Skladanowski, Resistance mechanisms associated with altered intracellular distribution of anticancer agents, Pharmacol. Ther. (2000), https://doi.org/10.1016/S0163-7258(99)00073-X.
[7] M.T. Kuo, Redox regulation of multidrug resistance in cancer chemotherapy: molecular mechanisms and therapeutic opportunities, Antioxidants Redox Signal. 11 (2009), https://doi.org/10.1089/ars.2008.2095.
[8] D. Penta, P. Mondal, J. Natesh, S.M. Meeran, Dietary bioactive diindolylmethane enhances the therapeutic efficacy of centchroman in breast cancer cells by regulating ABCB1/P-gp efflux transporter, J. Nutr. Biochem. 94 (2021), https://doi.org/10.1016/j.jnutbio.2021.108749.
[9] J. Škarda, M. Hajdúch, P. Flodr, E. Fridman, J. Kopolovic, V. Kolek, J. Klein, Z. Kolář, Drug resistance in lung cancer, Pharmacologyonline 3 (2007).
[10] A. Chang, Chemotherapy, chemoresistance and the changing treatment landscape for NSCLC, Lung Cancer (2011) 71, https://doi.org/10.1016/j.lungcan.2010.08.022.
[11] Q. Wu, Z. Yang, Y. Nie, Y. Shi, D. Fan, Multi-drug resistance in cancer chemotherapeutics: mechanisms and lab approaches, Cancer Lett. 347 (2014), https://doi.org/10.1016/j.canlet.2014.03.013.
[12] K. Nooter, F.T. Bosman, H. Burger, K.E. Van Wingerden, M.J. Flens, R.J. Scheper, R.G. Oostrum, A.W.M. Boersma, A. Van Der Gaast, G. Stoter, Expression of the multidrug resistance-associated protein (MRP) gene in primary non-small-cell lung cancer, Ann. Oncol. 7 (1996), https://doi.org/10.1093/oxfordjournals.annonc.a010484.
[13] B. Mansoori, A. Mohammadi, S. Davudian, S. Shirjang, B. Baradaran, The different mechanisms of cancer drug resistance: a brief review, Adv. Pharmaceut. Bull. 7 (2017), https://doi.org/10.15171/apb.2017.041.
[14] S. Donzelli, F. Mori, F. Biagioni, T. Bellissimo, C. Pulito, P. Muti, S. Strano, G. Blandino, MicroRNAs: short non-coding players in cancer chemoresistance, Mol. Cell. Ther. 2 (2014), https://doi.org/10.1186/2052-8426-2-16.
[15] E. Tsvetkova, G.D. Goss, Drug resistance and its significance for treatment decisions in non-small-cell lung cancer, Curr. Oncol. 19 (2012), https://doi.org/10.3747/co.19.1113.
[16] J.L. Lesnock, K.M. Darcy, C. Tian, J.A. Deloia, M.M. Thrall, C. Zahn, D. K. Armstrong, M.J. Birrer, T.C. Krivak, BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study, Br. J. Cancer 108 (2013), https://doi.org/10.1038/bjc.2013.70.
[17] M. Margeli, B. Cirauqui, E. Castella, G. Tapia, C. Costa, A. Gimenez-Capitan, A. Barnadas, M.S. Ronco, S. Benlloch, M. Taron, R. Rosell, The prognostic value of BRCA1 mRNA expression levels following neoadjuvant chemotherapy in breast cancer, PLoS One 5 (2010), https://doi.org/10.1371/journal.pone.0009499.
[18] L.Y. Li, Y. Di Guan, X.S. Chen, J.M. Yang, Y. Cheng, DNA repair pathways in cancer therapy and resistance, Front. Pharmacol. 11 (2021), https://doi.org/10.3389/fphar.2020.629266.
[19] B. Pan, B. Feng, Y. Chen, G. Huang, R. Wang, L. Chen, H. Song, MiR-200b regulates autophagy associated with chemoresistance in human lung adenocarcinoma, Oncotarget 6 (2015), https://doi.org/10.18632/oncotarget.5352.
[20] X. ling Guo, F. Hu, S. shan Zhang, Q. dong Zhao, C. Zong, F. Ye, S. wei Guo, J. wei Zhang, R. Li, M. chao Wu, L. xin Wei, Inhibition of p53 increases chemosensitivity to 5-FU in nutrient-deprived hepatocarcinoma cells by suppressing autophagy, Cancer Lett. 346 (2014), https://doi.org/10.1016/j.canlet.2014.01.011.
[21] W. Feng, C. Gao, W. Liu, H. Ren, C. Wang, K. Ge, S. Li, G. Zhou, H. Li, S. Wang, G. Jia, Z. Li, J. Zhang, A novel anticancer theranostic pro-prodrug based on hypoxia and photo sequential control, Chem. Commun. 52 (2016), https://doi.org/10.1039/c6cc02932a.
[22] S. Sarvi, A.C. Mackinnon, N. Avlonitis, M. Bradley, R.C. Rintoul, D.M. Rassl, W. Wang, S.J. Forbes, C.D. Gregory, T. Sethi, CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant but sensitive to a novel neuropeptide antagonist, Cancer Res. 74 (2014), https://doi.org/10.1158/0008-5472.CAN-13-1541.
[23] T.N. Kjær, M.J. Ornstrup, M.M. Poulsen, J.O.L. Jørgensen, D.M. Hougaard, A. S. Cohen, S. Neghabat, B. Richelsen, S.B. Pedersen, Resveratrol reduces the levels of circulating androgen precursors but has no effect on, testosterone, dihydrotestosterone, PSA levels or prostate volume. A 4-month randomised trial in middle-aged men, Prostate 75 (2015) 1255–1263, https://doi.org/10.1002/pros.23006.
[24] C.R. Arnold, J. Mangesius, I.I. Skvortsova, U. Ganswindt, The role of cancer stem cells in radiation resistance, Front. Oncol. 10 (2020), https://doi.org/10.3389/fonc.2020.00164.
[25] G. Liu, X. Yuan, Z. Zeng, P. Tunici, H. Ng, I.R. Abdulkadir, L. Lu, D. Irvin, K. L. Black, J.S. Yu, Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma, Mol. Cancer 5 (2006), https://doi.org/10.1186/1476-4598-5-67.
[26] L. Desiderato, M.W. Davey, A.A. Piper, Demethylation of the human MDR1 5′ region accompanies activation of P-glycoprotein expression in a HL60 multidrug resistant subline, Somat. Cell Mol. Genet. 23 (1997), https://doi.org/10.1007/BF02673749.
[27] T. Ivanova, H. Zouridis, Y. Wu, L.L. Cheng, I.B. Tan, V. Gopalakrishnan, C.H. Ooi, J. Lee, L. Qin, J. Wu, M. Lee, S.Y. Rha, D. Huang, N. Liem, K.G. Yeoh, W.P. Yong, B.T. Teh, P. Tan, Integrated epigenomics identifies BMP4 as a modulator of cisplatin sensitivity in gastric cancer, Gut 62 (2013), https://doi.org/10.1136/gutjnl-2011-301113.

[28] V. Martín, A.M. Sanchez-Sanchez, F. Herrera, C. Gomez-Manzano, J. Fueyo, M. A. Alvarez-Vega, I. Antolín, C. Rodriguez, Melatonin-induced methylation of the ABCG2/BCRP promoter as a novel mechanism to overcome multidrug resistance in brain tumour stem cells, Br. J. Cancer 108 (2013), https://doi.org/10.1038/bjc.2013.188.
[29] M. Farhan, M. Aatif, P. Dandawate, A. Ahmad, Non-coding RNAs as mediators of tamoxifen resistance in breast cancers, Adv. Exp. Med. Biol. (2019), https://doi.org/10.1007/978-3-030-20301-6_11.
[30] R. Adelaiye-Ogala, J. Budka, N.P. Damayanti, J. Arrington, M. Ferris, C.C. Hsu, S. Chintala, A. Orillion, K.M. Miles, L. Shen, M. Elbanna, E. Ciamporcero, S. Arisa, P. Pettazzoni, G.F. Draetta, M. Seshadri, B. Hancock, M. Radovich, J. Kota, M. Buck, H. Keilhack, B.P. McCarthy, S.A. Persohn, P.R. Territo, Y. Zang, J. Irudayaraj, W.A. Tao, P. Hollenhorst, R. Pili, EZH2 modifies sunitinib resistance in renal cell carcinoma by kinome reprogramming, Cancer Res. 77 (2017), https://doi.org/10.1158/0008-5472.CAN-17-0899.
[31] H. Huo, P.G. Magro, E. Christy Pietsch, B.B. Patel, K.W. Scotto, Histone methyltransferase MLL1 regulates MDR1 transcription and chemoresistance, Cancer Res. 70 (2010), https://doi.org/10.1158/0008-5472.CAN-10-0755.
[32] K. Dimopoulos, A. Søgaard Helbo, H. Fibiger Munch-Petersen, L. Sjö, J. Christensen, L. Sommer Kristensen, F. Asmar, N.E.U. Hermansen, C. O'Connel, P. Gimsing, G. Liang, K. Grønbæk, Dual inhibition of DNMTs and EZH2 can overcome both intrinsic and acquired resistance of myeloma cells to IMiDs in a cereblon-independent manner, Mol. Oncol. 12 (2018), https://doi.org/10.1002/1878-0261.12157.
[33] P. Mondal, S.M. Meeran, Long non-coding RNAs in breast cancer metastasis, Non-Coding RNA Res. 5 (2020), https://doi.org/10.1016/j.ncrna.2020.11.004.
[34] X. Chen, H. Zhu, W. Ye, Y. Cui, M. Chen, MicroRNA-29a enhances cisplatin sensitivity in non-small cell lung cancer through the regulation of REV3L, Mol. Med. Rep. 19 (2019), https://doi.org/10.3892/mmr.2018.9723.
[35] X. Lu, R. Liu, M. Wang, A.K. Kumar, F. Pan, L. He, Z. Hu, Z. Guo, MicroRNA-140 impedes DNA repair by targeting FEN1 and enhances chemotherapeutic response in breast cancer, Oncogene 39 (2020), https://doi.org/10.1038/s41388-019-0986-0.
[36] M. Farhan, A. Malik, M.F. Ullah, S. Afaq, M. Faisal, A.A. Farooqi, B. Biersack, R. Schobert, A. Ahmad, Garcinol sensitizes NSCLC cells to standard therapies by regulating EMT-modulating miRNAs, Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20040800.
[37] B. Kaur, Y. Mukhlis, J. Natesh, D. Penta, S. Musthapa Meeran, Identification of hub genes associated with EMT-induced chemoresistance in breast cancer using integrated bioinformatics analysis, Gene (2021), https://doi.org/10.1016/j.gene.2021.146016.
[38] J. Xie, F. Yu, D. Li, X. Zhu, X. Zhang, Z. Lv, MicroRNA-218 regulates cisplatin (DPP) chemosensitivity in non-small cell lung cancer by targeting RUNX2, Tumor Biol. 37 (2016), https://doi.org/10.1007/s13277-015-3831-2.
[39] L. Shi, Z. Xu, G. Wu, X. Chen, Y. Huang, Y. Wang, W. Jiang, B. Ke, Up-regulation of miR-146a increases the sensitivity of non-small cell lung cancer to DDP by downregulating cyclin J, BMC Cancer 17 (2017), https://doi.org/10.1186/s12885-017-3132-9.
[40] Y. Chen, Y. Song, Y. Mi, H. Jin, J. Cao, H. Li, L. Han, T. Huang, X. Zhang, S. Ren, Q. Ma, Z. Zou, microRNA-499a promotes the progression and chemoresistance of cervical cancer cells by targeting SOX6, Apoptosis (2020) 25, https://doi.org/10.1007/s10495-019-01588-y.
[41] M. Xie, Z. Fu, J. Cao, Y. Liu, J. Wu, Q. Li, Y. Chen, MicroRNA-132 and microRNA-212 mediate doxorubicin resistance by down-regulating the PTEN-AKT/NF-κB signaling pathway in breast cancer, Biomed. Pharmacother. 102 (2018), https://doi.org/10.1016/j.biopha.2018.03.088.
[42] Y.Z. Pan, M.E. Morris, A.M. Yu, MicroRNA-328 negatively regulates the expression of breast cancer resistance protein (BCRP/ABCG2) in human cancer cells, Mol. Pharmacol. 75 (2009), https://doi.org/10.1124/mol.108.054163.
[43] W.Q. Li, Y.M. Li, B.B. Tao, Y.C. Lu, G.H. Hu, H.M. Liu, J. He, Y. Xu, H.Y. Yu, Downregulation of ABCG2 expression in glioblastoma cancer stem cells with miRNA-328 may decrease their chemoresistance, Med. Sci. Monit. 16 (2010).
[44] W. Zhao, H. Li, S. Yang, D. Guo, J. Chen, S. Miao, Y. Xin, M. Liang, Microrna-152 suppresses cisplatin resistance in a549 cells, Oncol. Lett. 18 (2019), https://doi.org/10.3892/ol.2019.10834.
[45] H. Hu, Y. Wang, Z. Qin, W. Sun, Y. Chen, J. Wang, Y. Wang, J. Nie, L. Chen, S. Cai, L. Yu, S. Zeng, Regulation of mrp4 expression by circhipk3 via sponging mir-124-3p/mir-4524-5p in hepatocellular carcinoma, Biomedicines 9 (2021), https://doi.org/10.3390/biomedicines9050497.
[46] Y. Shang, B. Feng, L. Zhou, G. Ren, Z. Zhang, X. Fan, Y. Sun, G. Luo, J. Liang, K. Wu, Y. Nie, D. Fan, The miR27b-CCNG1-P53-miR-508-5p axis regulates multidrug resistance of gastric cancer, Oncotarget 7 (2016), https://doi.org/10.18632/ONCOTARGET.6374.
[47] Y. Shang, Z. Zhang, Z. Liu, B. Feng, G. Ren, K. Li, L. Zhou, Y. Sun, M. Li, J. Zhou, Y. An, K. Wu, Y. Nie, D. Fan, MiR-508-5p regulates multidrug resistance of gastric cancer by targeting ABCB1 and ZNRD1, Oncogene 33 (2014), https://doi.org/10.1038/onc.2013.297.
[48] Q. Wu, Z. Yang, L. Xia, Y. Nie, K. Wu, Y.S.D. Fan, Methylation of mir-129-5p cpg island modulates multi-drug resistance in gastric cancer by targeting abc transporters, Oncotarget 5 (2014), https://doi.org/10.18632/oncotarget.2594.
[49] R. Teng, Y. Hu, J. Zhou, B. Seifer, Y. Chen, J. Shen, L. Wang, Overexpression of Lin28 decreases the chemosensitivity of gastric cancer cells to oxaliplatin, paclitaxel, doxorubicin, and fluorouracil in part via microRNA-107, PLoS One 10 (2015), https://doi.org/10.1371/journal.pone.0143716.
[50] M. Zhan, Q. Qu, G. Wang, H. Zhou, Let-7c sensitizes acquired cisplatin-resistant A549 cells by targeting ABCC2 and Bcl-XL, Pharmazie 68 (2013), https://doi.org/10.1691/ph.2013.3538.
[51] K. Xu, X. Liang, K. Shen, D. Cui, Y. Zheng, J. Xu, Z. Fan, Y. Qiu, Q. Li, L. Ni, J. Liu, miR-297 modulates multidrug resistance in human colorectal carcinoma by down-regulating MRP-2, Biochem. J. 446 (2012), https://doi.org/10.1042/BJ20120386.
[52] F. Borel, R. Han, A. Visser, H. Petry, S.J.H. van Deventer, P.L.M. Jansen, P. Konstantinova, Adenosine triphosphate-binding cassette transporter genes up-regulation in untreated hepatocellular carcinoma is mediated by cellular microRNAs, Hepatology 55 (2012), https://doi.org/10.1002/hep.24682.
[53] P.X. Qian, A. Banerjee, Z.S. Wu, X. Zhang, H. Wang, V. Pandey, W.J. Zhang, X. F. Lv, S. Tan, P.E. Lobie, T. Zhu, Loss of SNAIL regulated miR-128-2 on chromosome 3p22.3 targets multiple stem cell factors to promote transformation of mammary epithelial cells, Cancer Res. 72 (2012), https://doi.org/10.1158/0008-5472.CAN-12-1507.
[54] Y. Zhu, F. Yu, Y. Jiao, J. Feng, W. Tang, H. Yao, C. Gong, J. Chen, F. Su, Y. Zhang, E. Song, Reduced miR-128 in breast tumor-initiating cells induces chemotherapeutic resistance via Bmi-1 and ABCC5, Clin. Cancer Res. 17 (2011), https://doi.org/10.1158/1078-0432.CCR-11-0071.
[55] J. Ma, T. Wang, R. Guo, X. Yang, J. Yin, J. Yu, Q. Xiang, X. Pan, H. Tang, X. Lei, Involvement of MIR-133a and MIR-326 in ADM resistance of HepG2 through modulating expression of ABCC1, J. Drug Target. 23 (2015), https://doi.org/10.3109/1061186X.2015.1015536.
[56] Z. Liang, H. Wu, J. Xia, Y. Li, Y. Zhang, K. Huang, N. Wagar, Y. Yoon, H.T. Cho, S. Scala, H. Shim, Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1, Biochem. Pharmacol. 79 (2010), https://doi.org/10.1016/j.bcp.2009.10.017.
[57] Z. Dong, L. Ren, L. Lin, J. Li, Y. Huang, J. Li, Effect of microRNA-21 on multidrug resistance reversal in A549/DDP human lung cancer cells, Mol. Med. Rep. 11 (2015), https://doi.org/10.3892/mmr.2014.2662.
[58] B. Jin, Y. Liu, H. Wang, Antagonism of miRNA-21 sensitizes human gastric cancer cells to paclitaxel, Cell Biochem. Biophys. 72 (2015), https://doi.org/10.1007/s12013-014-0450-2.
[59] Y.Z. Pan, A. Zhou, Z. Hu, A.M. Yu, Small nucleolar RNA-derived microRNA hsa-miR-1291 modulates cellular drug disposition through direct targeting of ABC transporter ABCC1, Drug Metab. Dispos. 41 (2013), https://doi.org/10.1124/dmd.113.052092.
[60] A. Armada, B.C. Gomes, M. Viveiros, J. Rueff, A.S. Rodrigues, Regulation of ABCB1 Activity by microRNA-200c and microRNA-203a in Breast Cancer Cells: the Quest for microRNAs' Involvement in Cancer Drug Resistance, vol. 2, Cancer Drug Resist, 2019, https://doi.org/10.20517/cdr.2019.24.
[61] L. Bao, S. Hazari, S. Mehra, D. Kaushal, K. Moroz, S. Dash, Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated by miR-298, Am. J. Pathol. 180 (2012), https://doi.org/10.1016/j.ajpath.2012.02.024.
[62] B. Wang, F.-Y. Lu, R.-H. Shi, Y.-D. Feng, X.-D. Zhao, Z.-P. Lu, L. Xiao, G.-Q. Zhou, J.-M. Qiu, C.-E. Cheng, MiR-26b regulates 5-FU-resistance in human colorectal cancer via down-regulation of Pgp, Am. J. Cancer Res. 8 (2018).
[63] L. Ding, J. Ni, F. Yang, L. Huang, H. Deng, Y. Wu, X. Ding, J. Tang, Promising therapeutic role of miR-27b in tumor, Tumor Biol. 39 (2017), https://doi.org/10.1177/1010428317691657.
[64] Q. Zhao, Y. Li, B.B. Tan, L.Q. Fan, P.G. Yang, Y. Tian, HIF-1α induces multidrug resistance in gastric cancer cells by inducing miR-27a, PLoS One 10 (2015), https://doi.org/10.1371/journal.pone.0132746.
[65] D.D. Feng, H. Zhang, P. Zhang, Y.S. Zheng, X.J. Zhang, B.W. Han, X.Q. Luo, L. Xu, H. Zhou, L.H. Qu, Y.Q. Chen, Down-regulated miR-331-5p and miR-27a are associated with chemotherapy resistance and relapse in leukaemia, J. Cell Mol. Med. 15 (2011), https://doi.org/10.1111/j.1582-4934.2010.01213.x.
[66] Z. Zou, R. Zou, D. Zong, Y. Shi, J. Chen, J. Huang, J. Zhu, L. Chen, X. Bao, Y. Liu, W. Liu, W. Huang, J. Hu, Z. Chen, X. Lao, C. Chen, X. Huang, Y. Lu, X. Ni, D. Fang, D. Wu, S. Lu, M. Jiang, C. Qiu, Y. Wu, Q. Qiu, Y. Dong, Y. Su, C. Zhao, Z. Zhong, J. Cai, Y. Liang, miR-495 sensitizes MDR cancer cells to the combination of doxorubicin and taxol by inhibiting MDR1 expression, J. Cell Mol. Med. 21 (2017), https://doi.org/10.1111/jcmm.13114.
[67] J.P. Gong, L. Yang, J.W. Tang, P. Sun, Q. Hu, J.W. Qin, X.M. Xu, B.C. Sun, J. H. Tang, Overexpression of microRNA-24 increases the sensitivity to paclitaxel in drug-resistant breast carcinoma cell lines via targeting ABCB9, Oncol. Lett. 12 (2016), https://doi.org/10.3892/ol.2016.5139.
[68] Z. Dong, Z. Zhong, L. Yang, S. Wang, Z. Gong, MicroRNA-31 inhibits cisplatin-induced apoptosis in non-small cell lung cancer cells by regulating the drug transporter ABCB9, Cancer Lett. 343 (2014), https://doi.org/10.1016/j.canlet.2013.09.034.
[69] K. Wu, Y. Yang, J. Zhao, S. Zhao, BAG3-mediated miRNA let-7g and let-7i inhibit proliferation and enhance apoptosis of human esophageal carcinoma cells by targeting the drug transporter ABCC10, Cancer Lett. 371 (2016), https://doi.org/10.1016/j.canlet.2015.11.031.
[70] Z. Fang, W. Chen, Z. Yuan, X. Liu, H. Jiang, LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRP1 and MDR1 via STAT3 activation, Biomed. Pharmacother. 101 (2018), https://doi.org/10.1016/j.biopha.2018.02.130.
[71] L.J. Tian, Y.P. Wu, D. Wang, Z.H. Zhou, S. Bin Xue, D.Y. Zhang, Y.G. Wei, W. Liu, Upregulation of long noncoding RNA (lncRNA) X-inactive specific transcript (XIST) is associated with cisplatin resistance in non-small cell lung cancer (NSCLC) by downregulating microRNA-144-3p, Med. Sci. Monit. 25 (2019), https://doi.org/10.12659/MSM.916075.

[72] D. Zhang, L. Ding, Y. Li, J. Ren, G. Shi, Y. Wang, S. Zhao, Y. Ni, Y. Hou, Midkine derived from cancer-associated fibroblasts promotes cisplatin-resistance via up-regulation of the expression of lncRNA ANRIL in tumour cells, Sci. Rep. 7 (2017), https://doi.org/10.1038/s41598-017-13431-y.
[73] B. Hu, H. Zhang, Z. Wang, F. Zhang, H. Wei, L. Li, LncRNA CCAT1/miR-130a-3p axis increases cisplatin resistance in non-small-cell lung cancer cell line by targeting SOX4, Cancer Biol. Ther. 18 (2017), https://doi.org/10.1080/15384047.2017.1385679.
[74] E. Turrini, S. Haenisch, S. Laechelt, T. Diewock, O. Bruhn, I. Cascorbi, MicroRNA profiling in K-562 cells under imatinib treatment: influence of miR-212 and miR-328 on ABCG2 expression, Pharmacogenetics Genom. 22 (2012), https://doi.org/10.1097/FPC.0b013e328350012b.
[75] H. Doktorova, J. Hrabeta, M.A. Khalil, T. Eckschlager, Hypoxia-induced chemoresistance in cancer cells: the role of not only HIF-1, Biomed, Pap. 159 (2015), https://doi.org/10.5507/bp.2015.025.
[76] H.S. Abyaneh, N. Gupta, A. Radziwon-Balicka, P. Jurasz, J. Seubert, R. Lai, A. Lavasanifar, STAT3 but not HIF-1α is important in mediating hypoxia-induced chemoresistance in MDA-MB-231, a triple negative breast cancer cell line, Cancers 9 (2017), https://doi.org/10.3390/cancers9100137.
[77] Y.A. Tang, Y. feng Chen, Y. Bao, S. Mahara, S.M.J.M. Yatim, G. Oguz, P.L. Lee, M. Feng, Y. Cai, E.Y. Tan, S.S. Fong, Z. huan Yang, P. Lan, X. jian Wu, Q. Yu, Hypoxic tumor microenvironment activates GLI2 via HIF-1α and TGF-β2 to promote chemoresistance in colorectal cancer, Proc. Natl. Acad. Sci. U. S. A. 115 (2018), https://doi.org/10.1073/pnas.1801348115.
[78] Y. Yan, F. Liu, L. Han, L. Zhao, J. Chen, O.I. Olopade, M. He, HIF-2α promotes conversion to a stem cell phenotype and induces chemoresistance in breast cancer cells by activating Wnt and Notch pathways, Integr. Vlsi J. 1 (2018) 107–112.
[79] D. Sabry, S.E.M. El-Deek, M. Maher, M.A.H. El-Baz, H.M. El-Bader, E. Amer, E. A. Hassan, W. Fathy, H.E.M. El-Deek, Role of miRNA-210, miRNA-21 and miRNA-126 as diagnostic biomarkers in colorectal carcinoma: impact of HIF-1α-VEGF signaling pathway, Mol. Cell. Biochem. 454 (2019), https://doi.org/10.1007/s11010-018-3462-1.
[80] X. Ge, X. Liu, F. Lin, P. Li, K. Liu, R. Geng, C. Dai, Y. Lin, W. Tang, Z. Wu, J. Chang, J. Lu, J. Li, MicroRNA-421 regulated by HIF-1α promotes metastasis, inhibits apoptosis, and induces cisplatin resistance by targeting E-cadherin and caspase-3 in gastric cancer, Oncotarget 7 (2016), https://doi.org/10.18632/oncotarget.8228.
[81] L. Chen, Q. Zhu, L. Lu, Y. Liu, MiR-132 inhibits migration and invasion and increases chemosensitivity of cisplatin-resistant oral squamous cell carcinoma cells via targeting TGF-β1, Bioengineered 11 (2020), https://doi.org/10.1080/21655979.2019.1710925.
[82] W. Song, S. Wu, Q. Wu, L. Zhou, L. Yu, B. Zhu, X. Gong, The microRNA-141-3p/CDK8 pathway regulates the chemosensitivity of breast cancer cells to trastuzumab, J. Cell. Biochem. 120 (2019), https://doi.org/10.1002/jcb.28685.
[83] X. Li, Y. Wu, A. Liu, X. Tang, Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1α feedback regulatory loop, Tumor Biol. 37 (2016) 14733–14743, https://doi.org/10.1007/s13277-016-5348-8.
[84] Y. Shan, X. Li, B. You, S. Shi, Q. Zhang, Y. You, MicroRNA-338 inhibits migration and proliferation by targeting hypoxia-induced factor 1α in nasopharyngeal carcinoma, Oncol. Rep. 34 (2015) 1943–1952, https://doi.org/10.3892/or.2015.4195.
[85] A. Keremu, A. Aini, Y. Maimaitirexiati, Z. Liang, P. Aila, P. Xierela, A. Tusun, H. Moming, A. Yusufu, Overcoming cisplatin resistance in osteosarcoma through the miR-199a-modulated inhibition of HIF-1α, Biosci. Rep. 39 (2019) 1–11, https://doi.org/10.1042/BSR20170080.
[86] Z. Xie, L. Cao, J. Zhang, miR-21 modulates paclitaxel sensitivity and hypoxia-inducible factor-1α expression in human ovarian cancer cells, Oncol. Lett. 6 (2013) 795–800, https://doi.org/10.3892/ol.2013.1432.
[87] C. Li, J. Zhao, W. Sun, microRNA-222-Mediated VHL downregulation facilitates retinoblastoma chemoresistance by increasing hif1α expression, Investig. Ophthalmol. Vis. Sci. 61 (2020), https://doi.org/10.1167/IOVS.61.10.9.
[88] H. Li, M. Rokavec, L. Jiang, D. Horst, H. Hermeking, Antagonistic Effects of P53 and HIF1A on microRNA-34a Regulation of PPP1R11 and STAT3 and Hypoxia-Induced Epithelial to Mesenchymal Transition in Colorectal Cancer Cells, Elsevier Inc., 2017, https://doi.org/10.1053/j.gastro.2017.04.017.
[89] P. Wang, Q. Yan, B. Liao, L. Zhao, S. Xiong, J. Wang, D. Zou, J. Pan, L. Wu, Y. Deng, N. Wu, S. Gong, The HIF1α/HIF2α-miR210-3p network regulates glioblastoma cell proliferation, dedifferentiation and chemoresistance through EGF under hypoxic conditions, Cell Death Dis. 11 (2020), https://doi.org/10.1038/s41419-020-03150-0.
[90] K. Xu, Y. Zhan, Z. Yuan, Y. Qiu, H. Wang, G. Fan, J. Wang, W. Li, Y. Cao, X. Shen, J. Zhang, X. Liang, P. Yin, Hypoxia induces drug resistance in colorectal cancer through the HIF-1α/miR-338-5p/IL-6 feedback loop, Mol. Ther. 27 (2019), https://doi.org/10.1016/j.ymthe.2019.05.017.
[91] S. Huang, P. Qi, T. Zhang, F. Li, X. He, The HIF_1α/miR_224_3p/ATG5 axis affects cell mobility and chemosensitivity by regulating hypoxia_induced protective autophagy in glioblastoma and astrocytoma, Oncol. Rep. 41 (2019) 1759–1768, https://doi.org/10.3892/or.2018.6929.
[92] C.B. Trelford, G.M. Di Guglielmo, Molecular mechanisms of mammalian autophagy, Biochem. J. 478 (2021), https://doi.org/10.1042/BCJ20210314.
[93] R. Ojha, S. Bhattacharyya, S.K. Singh, Autophagy in cancer stem cells: a potential link between chemoresistance, recurrence, and metastasis, Biores. Open Access 4 (2015), https://doi.org/10.1089/biores.2014.0035.
[94] X. Li, Y. Zhou, Y. Li, L. Yang, Y. Ma, X. Peng, S. Yang, J. Liu, H. Li, Autophagy: a novel mechanism of chemoresistance in cancers, Biomed. Pharmacother. 119 (2019), https://doi.org/10.1016/j.biopha.2019.109415.
[95] J. Liu, Y. Xing, L. Rong, MiR-181 regulates cisplatin-resistant non-small cell lung cancer via downregulation of autophagy through the PTEN/PI3K/AKT pathway, Oncol. Rep. 39 (2018), https://doi.org/10.3892/or.2018.6268.
[96] H. Zhang, B. Hu, Z. Wang, F. Zhang, H. Wei, L. Li, miR-181c contributes to cisplatin resistance in non-small cell lung cancer cells by targeting Wnt inhibition factor 1, Cancer Chemother, Pharmacol 80 (2017), https://doi.org/10.1007/s00280-017-3435-1.
[97] W. Sun, J. Li, L. Zhou, J. Han, R. Liu, H. Zhang, T. Ning, Z. Gao, B. Liu, X. Chen, Y. Ba, The c-Myc/miR-27b-3p/ATG10 regulatory axis regulates chemoresistance in colorectal cancer, Theranostics 10 (2020), https://doi.org/10.7150/thno.37621.
[98] S. Wu, X. Wang, J. Chen, Y. Chen, Autophagy of cancer stem cells is involved with chemoresistance of colon cancer cells, Biochem. Biophys. Res. Commun. 434 (2013), https://doi.org/10.1016/j.bbrc.2013.04.053.
[99] A. Belounis, C. Nyalendo, R. Le Gall, T.V. Imbriglio, M. Mahma, P. Teira, M. Beaunoyer, S. Cournoyer, E. Haddad, G. Vassal, H. Sartelet, Autophagy is associated with chemoresistance in neuroblastoma, BMC Cancer 16 (2016), https://doi.org/10.1186/s12885-016-2906-9.
[100] R. Xu, S. Liu, H. Hong Chen, L. Lao, MicroRNA-30a downregulation contributes to chemoresistance of osteosarcoma cells through activating Beclin-1-mediated autophagy, Oncol. Rep. 35 (2016), https://doi.org/10.3892/or.2015.4497.
[101] Z. Wang, N. Wang, P. Liu, Q. Chen, H. Situ, T. Xie, J. Zhang, C. Peng, Y. Lin, J. Chen, MicroRNA-25 regulates chemoresistance-associated autophagy in breast cancer cells, a process modulated by the natural autophagy inducer isoliquiritigenin, Oncotarget 5 (2014), https://doi.org/10.18632/oncotarget.2192.
[102] B. Pan, Y. Chen, H. Song, Y. Xu, R. Wang, L. Chen, Mir-24-3p downregulation contributes to VP16-DDP resistance in small-cell lung cancer by targeting ATG4A, Oncotarget 6 (2015), https://doi.org/10.18632/oncotarget.2787.
[103] W. Tan, Y. Liao, Y. Qiu, H. Liu, D. Tan, T. Wu, M. Tang, S. Zhang, H. Wang, miRNA 146a promotes chemotherapy resistance in lung cancer cells by targeting DNA damage inducible transcript 3 (CHOP), Cancer Lett. 428 (2018), https://doi.org/10.1016/j.canlet.2018.04.028.
[104] X. Li, M.T. Lewis, J. Huang, C. Gutierrez, C.K. Osborne, M.F. Wu, S.G. Hilsenbeck, A. Pavlick, X. Zhang, G.C. Chamness, H. Wong, J. Rosen, J.C. Chang, Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy, J. Natl. Cancer Inst. 100 (2008), https://doi.org/10.1093/jnci/djn123.
[105] Y. Shimono, M. Zabala, R.W. Cho, N. Lobo, P. Dalerba, D. Qian, M. Diehn, H. Liu, S.P. Panula, E. Chiao, F.M. Dirbas, G. Somlo, R.A.R. Pera, K. Lao, M.F. Clarke, Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells, Cell 138 (2009), https://doi.org/10.1016/j.cell.2009.07.011.
[106] C. Liu, K. Kelnar, A.V. Vlassov, D. Brown, J. Wang, D.G. Tang, Distinct microRNA expression profiles in prostate cancer stem/progenitor cells and tumor-suppressive functions of let-7, Cancer Res. 72 (2012), https://doi.org/10.1158/0008-5472.CAN-11-3864.
[107] C. Ma, T. Huang, Y.C. Ding, W. Yu, Q. Wang, B. Meng, S.X. Luo, MicroRNA-200c overexpression inhibits chemoresistance, invasion and colony formation of human pancreatic cancer stem cells, Int. J. Clin. Exp. Pathol. 8 (2015).
[108] J.F. Zeng, X.Q. Ma, L.P. Wang, W. Wei, MicroRNA-145 exerts tumor-suppressive and chemoresistance lowering effects by targeting CD44 in gastric cancer, World J. Gastroenterol. 23 (2017), https://doi.org/10.3748/wjg.v23.i13.2337.
[109] X. Sun, Y. Li, M. Zheng, W. Zuo, W. Zheng, MicroRNA-223 increases the sensitivity of triple-negative breast cancer stem cells to TRAIL-Induced apoptosis by targeting HAX-1, PLoS One 11 (2016), https://doi.org/10.1371/journal.pone.0162754.
[110] X. Zhang, G. Wan, S. Mlotshwa, V. Vance, F.G. Berger, H. Chen, X. Lu, Oncogenic Wip1 phosphatase is inhibited by miR-16 in the DNA damage signaling pathway, Cancer Res. 70 (2010), https://doi.org/10.1158/0008-5472.CAN-10-0697.
[111] J. Chen, X. Fu, Y. Wan, Z. Wang, D. Jiang, L. Shi, miR-125b inhibitor enhance the chemosensitivity of glioblastoma stem cells to temozolomide by targeting Bak1, Tumor Biol. 35 (2014), https://doi.org/10.1007/s13277-014-1821-4.
[112] L. Yang, Z. Lin, Y. Wang, S. Gao, Q. Li, C. Li, W. Xu, J. Chen, T. Liu, Z. Song, G. Liu, MiR-5100 increases the cisplatin resistance of the lung cancer stem cells by inhibiting the Rab6, Mol. Carcinog. 57 (2018), https://doi.org/10.1002/mc.22765.
[113] J.Y. Jeong, H. Kang, T.H. Kim, G. Kim, J.H. Heo, A.Y. Kwon, S. Kim, S. geun Jung, H.J. An, MicroRNA-136 inhibits cancer stem cell activity and enhances the anti-tumor effect of paclitaxel against chemoresistant ovarian cancer cells by targeting Notch3, Cancer Lett. 386 (2017), https://doi.org/10.1016/j.canlet.2016.11.017.
[114] X. Wang, Q. Meng, W. Qiao, R. Ma, W. Ju, J. Hu, H. Lu, J. Cui, Z. Jin, Y. Zhao, Y. Wang, miR-181b/Notch2 overcome chemoresistance by regulating cancer stem cell-like properties in NSCLC, Stem Cell Res. Ther. 9 (2018) 1–14, https://doi.org/10.1186/s13287-018-1072-1.
[115] E.Y. Park, E.S. Chang, E.J. Lee, H.W. Lee, H.G. Kang, K.H. Chun, Y.M. Woo, H. K. Kong, J.Y. Ko, H. Suzuki, E. Song, J.H. Park, Targeting of miR34a-NOTCH1 axis reduced breast cancer stemness and chemoresistance, Cancer Res. 74 (2014), https://doi.org/10.1158/0008-5472.CAN-14-1140.
[116] N. Sakamoto, R. Honma, Y. Sekino, K. Goto, K. Sentani, A. Ishikawa, N. Oue, W. Yasui, Non-coding RNAs are promising targets for stem cell-based cancer therapy, Non-Coding RNA Res. 2 (2017), https://doi.org/10.1016/j.ncrna.2017.05.002.
[117] A. Ahmad, Non-coding RNAs: a tale of junk turning into treasure, Non-Coding RNA Res. 1 (2016), https://doi.org/10.1016/j.ncrna.2016.12.001.

[118] P. Mondal, B. Kaur, J. Natesh, S.M. Meeran, The emerging role of miRNA in the perturbation of tumor immune microenvironment in chemoresistance: therapeutic implications, Semin. Cell Dev. Biol. (2021), https://doi.org/10.1016/j.semcdb.2021.04.001.

[119] P. Mondal, S.M. Meeran, Dietary regulation of miRNA in precision medicine of lung cancer, in: Epigenetics Precis. Med., Elsevier, 2022, pp. 513–542.

[120] C. Borga, S.M. Meeran, M. Fassan, Non-coding RNAs, a Real Next-Gen Class of Biomarkers? Non-Coding RNA Res., 2019 https://doi.org/10.1016/j.ncrna.2019.10.001.