Contribution of MicroRNAs in Chemoresistance to Cisplatin in the Top Five Deadliest Cancer: An Updated Review

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Cisplatin (DDP) is a well-known anticancer drug used for the treatment of numerous human cancers in solid organs, including bladder, breast, cervical, head and neck squamous cell, ovarian, among others. Its most important mode of action is the DNA-platinum adducts formation, inducing DNA damage response, silencing or activating several genes to induce apoptosis; these mechanisms result in genetics and epigenetics modifications. The ability of DDP to induce tumor cell death is often challenged by the presence of anti-apoptotic regulators, leading to chemoresistance, wherein many patients who have or will develop DDP-resistance. Cancer cells resist the apoptotic effect of chemotherapy, being a problem that severely restricts the successful results of treatment for many human cancers. In the last 30 years, researchers have discovered there are several types of RNAs, and among the most important are non-coding RNAs (ncRNAs), a class of RNAs that are not involved in protein production, but they are implicated in gene expression regulation, and representing the 98% of the human genome non-translated. Some ncRNAs of great interest are long ncRNAs, circular RNAs, and microRNAs (miRs). Accumulating studies reveal that aberrant miRs expression can affect the development of chemotherapy drug resistance, by modulating the expression of relevant target proteins. Thus, identifying molecular mechanisms underlying chemoresistance development is fundamental for setting strategies to improve the prognosis of patients with different types of cancer. Therefore, this review aimed to identify and summarize miRs that modulate chemoresistance in DDP-resistant in the top five deadliest cancer, both in vitro and in vivo human models.

Keywords: microRNA, drug-resistance, cisplatin, sensitivity, cancer

1 INTRODUCTION

Globally, cancer is the first leading cause of death. In 2020, 19.3 million new cases of cancer and almost 10 million deaths from cancer (Ferlay et al., 2021; Sung et al., 2021). Cisplatin [cis-diaminedichloroplatinum (II), DDP], discovered by Rosenberg and his colleagues in 1965 (Rosenberg et al., 1969), was the first platinum compound approved by FDA for cancer treatment in the United States in 1978 (FDA, 1978). It is a well-known chemotherapeutic drug
used for the treatment of numerous human cancer in solid organs, including head and neck, testis, small cells and non-small cells lung cancer, ovarian, cervical, and bladder. Once DDP crosses the cytosol, the low concentration of chloride present triggers two hydrolyses of the DDP, forming positively charged DDP derivative, which binds to negatively charged DNA bases, inducing DNA damage by forming DNA-platinum adducts, and simultaneously initiating self-defense mechanisms to activate or silence multiple genes, resulting in DNA damage response and repair pathways (Hu et al., 2016), cell cycle arrest (Velma et al., 2016) and DDP-induced apoptosis (Tanida et al., 2012). However, treatment response to DDP differs, and the main problem to its effectiveness is the development of drug resistance (Amable, 2016; Ko and Li, 2019). Cisplatin-resistance is inferred mainly when the usual clinical dose of DDP is magnified in drug-intensive therapy protocols and may require cytotoxic concentrations as much as 50–100-fold in addition to those needed for sensitive cells (Siddik, 1999). In fact, any factor that influences those processes can lead to the development of resistance to DDP. Moreover, drug resistance is responsible for over 90% of deaths in cancer patients receiving traditional chemotherapeutic drugs (Bukowski et al., 2020). Besides, the epithelial-mesenchymal transition (EMT) process contributes to chemoresistance by transforming epithelial cells into mesenchymal cells and altering cell-cell adhesion as well as the cellular extracellular matrix, leading to invasion of tumor cells (Ashrafizadeh et al., 2020). Autophagy, a process which degrades and recycles cellular proteins and organelles in response to cellular stresses, has been shown to attenuate the sensitivity of therapeutic drugs, protecting cancerous cells from death (Li W. et al., 2019). Thus, there is a crucial necessity to comprehend the underlying molecular mechanisms and recognize strategies to counteract DDP and facilitate predictions of the clinical response to therapy.

Non-coding RNAs are molecules that regulate gene expression under physiological and pathological conditions (Virginie et al., 2019) and are further divided into two principal groups, small ncRNAs (shorter than 200 bp) and long ncRNA (longer than 200 bp). MicroRNAs as a class of small ncRNAs, are a kind of short-chain, linear, approximately 21–25 nucleotides long that negatively regulate gene targets the post-transcriptional level by perfect complementarity of their “seed” region to 3′-UTR of its target mRNA, inducing their degradation. If there is a mismatch or imperfect complementarity, it results in translational repression (Guo et al., 2019). The latest release of the miRbase database (v22) contains 2654 human mature miRs sequences (Kozomara et al., 2019), which confirms their importance on gene expression regulation. Not surprisingly, atypical expression and/or activity of ncRNAs can affect the outcome of cancer treatment and allow tumors to acquire drug-resistant phenotypes (Yo et al., 2012; Tang et al., 2020). An increasing number of studies have shown that ncRNAs play an essential role in several types of cancer and miRs have been associated with DDP resistance, making them important potential therapeutic targets. So, in this narrative review, we summarize the current literature on the contribution of miRs that modulate chemoresistance to DDP in the top five deadliest cancer reported in 2020, some strategies to sensitize DDP-cells and reduce their malignant capacities, both in vitro and in vivo human models.

2 THE TOP FIVE DEADLIEST CANCER

The most common cause of cancer death for about 13% of total cancer diagnoses remains by far lung cancer (Ferlay et al., 2021; Sung et al., 2021). The global incidence of lung cancer estimated in 2020 was approximately 2206800 new cases and 1796100 cancer deaths (Figure 1). In terms of clinical and tumor genetics, lung cancer can be divided into small and non-small cell lung cancer. Non-small cell lung cancer (NSCLC) represents about 80%–95% of all diagnosed lung cancer cases, and NSCLC remains the leading cause of cancer death worldwide. The efficacy of DDP-based chemotherapy in cancer is limited by the occurrence of innate and acquired drug resistance and acquired resistance of NSCLC cells against cisplatin is the consequence of altered signaling leading to reduced G2/M cell cycle arrest and apoptosis (Sarin et al., 2017). On the other hand, small-cell lung cancer (SCLC) is a distinct form of lung cancer with unique clinical and histological characteristics, representing 10%–15% of all new cases of lung cancer, and SCLC cancer tends to grow and spread faster than NSCLC (Kitamura et al., 2009). SCLC is highly sensitive to the initial cycle of chemotherapy and, in many cases chemotherapy-resistant SCLC emerges, leading to rapid patient mortality. DDP-resistance in lung cancer can be induced by alterations to a huge number of intracellular pathways, where miRNAs play a vital role (Table 1), even though very few studies have demonstrated the role of miR on DDP-resistance in SCLC.

Followed by lung cancer, the second cause of cancer death is due to liver cancer (Ferlay et al., 2021; Sung et al., 2021). Liver cancer comprises a heterogeneous group of malignant liver tumors with different histological features and an unfavorable prognosis (Anwanwan et al., 2020). The global incidence of liver cancer estimated in 2020 was approximately 905700 new cases and 830200 cancer deaths (Figure 1). The prognosis for liver cancer is poor, due to merely 5%–15% of patients are eligible for surgical removal, because of diminished hepatic regenerative capacity (Anwanwan et al., 2020). Treatment options for more advanced stages include chemotherapy, however, fewer than one-third of patients benefit from the treatment, and drug resistance is evident within 6 months of initiating the regimen (El-Serag et al., 2008). On this basis, miRs have been involved in DDP-resistance in lung cancer and will be listed in Table 2.

Followed by liver cancer, the third cause of cancer death is due to stomach cancer (Ferlay et al., 2021; Sung et al., 2021). Gastric cancer is one of the most commonly diagnosed malignancies. The global incidence of stomach cancer estimated in 2020 was approximately 1089100 new cases and 768800 cancer deaths (Figure 1). In recent years, a rising body of evidence has revealed that miRs are dysregulated in almost all types of tumors, including gastric, modulating the proliferation, stemness, tumor immune escape, invasion, angiogenesis, and drug resistance of tumor cells (Chen et al., 2021). Some
studies in which miRs play a major role in mediating DDP-resistant stomach cancer will be detailed in Table 3.

After stomach cancer, the fourth cause of cancer mortality is due to breast cancer (Ferlay et al., 2021; Sung et al., 2021). Breast cancer is the most commonly diagnosed cancer worldwide and female breast cancer is the most commonly diagnosed cancer (Sung et al., 2021). The global incidence estimated in 2020 was approximately 2261400 new cases and 685000 cancer deaths due to breast cancer (Figure 1). Cisplatin is currently the most effective drug used to treat breast cancer; however, DDP-resistance presents a major challenge in the successful treatment of breast cancer. Breast cancer can be invasive or non-invasive. Invasive breast cancer is cancer that spreads into adjacent tissues and/or distant organs, while non-invasive breast cancer does not go beyond the milk ducts or lobules in the breast (Beikman et al., 2013). Some studies in which miRs play a major role in mediating DDP-resistant breast cancer will be detailed on Table 4.

The last cause of cancer mortality is due to colorectal cancer. Colorectal cancer starts when normal cells in the lining of the colon or rectum change and grow out of control, forming a mass called a tumor (Weitz et al., 2005). The global incidence of colon and rectum cancer estimated in 2020 was approximately 1880700 new cases and 915900 cancer deaths (Figure 1). The relative survival rate for colorectal cancer is 64% at 5-year following diagnosis and 58% at 10 years (Siegel et al., 2020). This can be determined by resistance to DDP, which may compromise the efficacy of chemotherapy, and some miRs related are described in Table 5.
### TABLE 1 | MicroRNAs involved in DDP-chemoresistance in lung cancer.

| miR     | Target     | Model                                | Expression | References          |
|---------|------------|--------------------------------------|------------|---------------------|
| miR-1   | ATG3       | in vitro: A-549 & NCI-H1299 cells     | Down       | Hua et al. (2018)   |
| miR-7   | Bcl-2      | in vitro: SPC-A1 cells               | Down       | Cheng et al. (2017) |
| miR-10a | PK3CA      | in vitro: A-549 & NCI-H1299 cells     | Up         | Huang T. et al. (2020) |
| miR-15b | STAT3, STAT5 | in vitro: A-549/DDP cells            | Up         | Sun et al. (2015)   |
| miR-17  | ATG7       | in vitro: A-549/DDP & NCI-H1299/DDP cells | Down       | Huang FX et al. (2019) |
| miR-18a | IRF-2      | in vitro: NCI-H226/DDP & A-549/DDP cells | Up         | Xiao and He. (2020) |
| miR-19a | PTEN       | in vitro: Lung biopsies of 85 non-small cell lung cancer patients | Up         | Xiao et al. (2018) |
| miR-21  | PTEN       | in vitro: A-549/DDP & NCI-H1460/DDP cells | Up         | Xiao et al. (2020) |
| miR-25  | Cyclin E2  | in vitro: NCI-H1146, NCI-H209, NCI-H446, NCI-H510A & NCI-H889 cells | Up         | Liang et al. (2021) |
| miR-25-3p | PTEN       | in vitro: A-549/DDP & NCI-H1299/DDP cells | Up         | Zhao et al. (2014) |
| miR-26a | HMGA2      | in vitro: A-549/DDP cells            | Down       | Yang et al. (2016)  |
| miR-29a | REV3L      | in vitro: A-549/DDP cells            | Down       | Chen et al. (2019b) |
| miR-29b-3p | COL1A1    | in vitro: A-549/DDP cells            | Down       | Jia and Wang. (2020) |
| miR-31  | ABCB9      | in vitro: Lung biopsies of 85 non-small cell lung cancer patients | Up         | Dong et al. (2014)  |
| miR-32  | ROBO1      | in vitro: NCI-H1460, A-549 & SK-MES-1 cells | Down       | Zheng et al. (2021b) |
| miR-34a-5p | TRIM29    | in vitro: HCC287, NCI-H522 & NCI-H23 cells | Down       | Luo et al. (2020)   |
| miR-96  | LMO7       | in vitro: A-549, PC-9 & NCI-H1299 cells | Up         | Wu et al. (2017)    |
| miR-98-5p | CTR1       | in vitro: A-549/DDP cells            | Up         | Jiang et al. (2016) |
| miR-100-5p | mTOR      | in vitro: A-549/DDP cells            | Down       | Qin et al. (2017)   |
| miR-101-3p | MCL-1      | in vitro: A-549 and NCI-H1299 cells | Down       | Wang et al. (2018)  |
| miR-34a-5p | TRIM29    | in vitro: A-549/DDP cells            | Down       | Hua et al. (2021)   |
| miR-103a-3p | NF-1      | in vitro: A-549/DDP cells            | Up         | Zhu et al. (2020a)  |
| miR-106a | ABCA1      | in vitro: A-549/DDP cells            | Up         | Ma et al. (2015)    |
| miR-106b-5p | PKD2      | in vitro: A-549/DDP cells            | Down       | Yu et al. (2017)    |
| miR-127-3p | MDM2      | in vitro: A-549/DDP & NCI-H1299/DDP cells | Down       | Zeng et al. (2020)  |
| miR-128-2 | EZF5       | in vitro: A-549 cells               | Up         | Donzelli et al. (2012) |
| miR-130b | PTEN       | in vitro: A-549/DDP & NCI-H446/DDP cells | Down       | Zhang et al. (2018) |
| miR-133b | GSTP1      | in vitro: A-549/DDP & NCI-H1299/DDP cells | Down       | Lin et al. (2018)   |
| miR-134 | FOXM1      | in vitro: A-549/DDP cells            | Down       | Li et al. (2017)    |
| miR-138-5p | ATG7      | in vitro: A-549/DDP cells            | Down       | Pan et al. (2019)   |
| miR-140-3p | Wnt/β-catenin | in vitro: A-549, NCI-H1299, NCI-H292 & Calu-3 cells | Down       | Wu et al. (2020b)   |
| miR-142-5p | PO-L1     | in vitro: A-549/DDP & HCC287/DDP cells | Down       | Zhu et al. (2021)   |
| miR-144-3p | Not reported | in vitro: A-549/CCD & NCI-H460/DDP cells | Down       | Tian et al. (2019)  |
| miR-145 | CDK6       | in vitro: Calu-6 & Calu-6/DDP cells | Up         | Bar et al. (2015)   |
|         | KLF4       | in vitro: A-549/DDP cells            | Down       | Cui et al. (2018)   |
| miR-146a | Not reported | in vitro: A-549/DDP cells | Down       | Zhang et al. (2019) |
|         | JNK-2      | in vitro: A-549/DDP cells            | Down       | Pang et al. (2017)  |
|         | NF-κB1     | in vitro: A-549/DDP & Calu-1/DDP     | Down       | Jiang et al. (2017a) |

(Continued on following page)
| miR        | Target       | Model                                      | Expression | References                  |
|------------|--------------|--------------------------------------------|------------|-----------------------------|
| miR-148b   | DNMT1        | in vivo: 28 non-small cell lung cancer tissues from patients | Down       | Sui et al. (2015)           |
| miR-149-5p | DCLK1        | in vitro: A-549/DDP & SPC-A1/DDP cells      | Down       | Zhu et al. (2020)           |
| miR-152    | Bcl-2, NF-κB | in vivo: 70 samples of patients with non-small cell lung cancer | Down       | Zhao et al. (2019)          |
| miR-185-5p | ABCC1        | in vitro: A-549/DDP & A-549/DDP cells       | Down       | Seidl et al. (2020)         |
| miR-186-5p | SIX1         | in vitro: A-549/DDP & NCI-H1299/DDP cells   | Down       | Pei et al. (2016)           |
| miR-195-5p | CHEK1        | in vitro: A-549 & NCI-H1299 cells           | Down       | Liu et al. (2020b)          |
| miR-196a   | Not reported | in vitro: A-549/DDP cells                   | Up         | Li et al. (2016a)           |
| miR-200a   | β-catenin    | in vitro: A-549/DDP cells                  | Down       | Tang et al. (2020)          |
| miR-200b   | Bcl-2, XIAP  | in vitro: A-549/DDP cells                  | Down       | Sun et al. (2012)           |
| miR-206    | No Reported  | in vitro: Calu-1, NCI-H520, SK-MES-1, H596, Calu-3, NCI-H652, NCI-H1395, NCI-H1299 & NCI-H460 cells lines | Down       | Ceppi et al. (2010)         |
| miR-200c   | ERCC3, ERCC4 | in vitro: SGC-7901/DDP cells               | Down       | Li et al. (2019a)           |
| miR-202    | KRAS         | in vitro: NCI-H441 & A-549 cells            | Down       | Sun et al. (2018)           |
| miR-206    | P-gp         | in vitro: A-549/DDP cells                  | Down       | Shen et al. (2020a)         |
| miR-216b   | Bcl-in-1     | in vitro: A-549/DDP cells                  | Down       | Chen et al. (2016b)         |
| miR-217    | LPPP         | in vitro: A-549/DDP cells                  | Up         | Yang et al. (2021)          |
| miR-219a   | FGF9         | in vitro: A-549/DDP & SPC-A1/DDP cells      | Down       | Rao et al. (2019)           |
| miR-223    | FBXW7        | in vitro: A-549, NCI-H588 & NCI-H1299 cells | Up         | Wang et al. (2020b)         |
| miR-326    | WNT2B        | in vitro: NCI-H358, A-549, NCI-H1299 & NCI-H1650 cells | Down       | Wu et al. (2020c)           |
| miR-330-5p | DCLK1        | in vitro: A-549 & NCI-H1299/DDP cells       | Down       | Ge et al. (2021)            |
| miR-377-3p | GOT1         | in vitro: A-549/DDP, NCI-H1299/DDP & Calu-3/DDP cells | Down       | Zhu et al. (2020b)          |
| miR-381    | ID-1         | in vitro: A-549, A-549/DDP & NCI-H460 cells | Down       | Huang et al. (2018)         |
| miR-383    | RBM24        | in vitro: A-549/DDP cells                  | Down       | He et al. (2021)            |
| miR-429    | Bcl-2, XIAP  | in vitro: A-549/DDP cells                  | Down       | Zhu et al. (2012a)          |
| miR-432    | E2F3, AXL    | in vitro: A-549 & NCI-H1299 cells           | Down       | Chen et al. (2016a)         |
| miR-448    | SATB1        | in vitro: A-549/DDP cells                  | Down       | Ning et al. (2020)          |
| miR-451    | Not reported | in vitro: A-549 cells                      | Down       | Bian et al. (2011)          |
| miR-454-3p | STAT3        | in vitro: A-549/DDP & H157/DDP cells        | Down       | Wang et al. (2019a)         |
| miR-486-5p | TWF1         | in vitro: A-549/DDP cells                  | Down       | Zhao et al. (2018)          |
| miR-493    | TCRP1        | in vitro: A-549/DDP cells                  | Down       | Jin et al. (2019)           |
| miR-497    | Bcl-2        | in vitro: A-549/DDP cells                  | Down       | Gu et al. (2017)            |
| miR-503    | FANCA        | in vitro: A-549, NCI-H446, NCI-H1650 & NCI-H1299 cells | Down       | Zhu et al. (2012b)          |
| miR-514a-3p| ULK1         | in vitro: A-549/DDP cells                  | Down       | Li et al. (2014)            |
| miR-519    | ZBTB5        | in vitro: A-549/DDP & A-549/DDP cells       | Down       | Shen et al. (2020b)         |
| miR-548a   | ROBO1        | in vitro: A-549/DDP & NCI-H1299/DDP cells   | Down       | Zheng et al. (2021b)        |
| miR-556-5p | NLRP3        | in vitro: A-549/DDP & NCI-H1299/DDP cells   | Down       | Shi et al. (2021)           |
| miR-630    | Bcl-2        | in vitro: A-549, NCI-H23, A-549, NCI-H1299, TL-4 & CL1-0 cells | Down       | Chen et al. (2018)          |
cells (Zheng J. et al., 2021). In the same way, tankyrase 1 and 2 activity of the TNKS1/2 are regulators of Wnt signaling by controlling the expression of KLF12 results in increased ability of lung cancer cells to form tumors (Godin-Heymann et al., 2016).

**3.1 MicroRNAs Involved in Cell Cycle**

**DDP-CHEMORESISTANCE**

| miR Target | Model | Expression | References |
|------------|-------|------------|------------|
| let-7i | BAG-1 | Up | Sun et al. (2017) |
| miR-4458 | REV3L | Up | Song et al. (2021) |
| miR-326 | RUNX2 | Down | Zhao et al. (2020b) |
| miR-1244 | TP53 | Down | Li et al. (2016b) |
| miR-641 | HOXA9 | Down | Wang et al. (2020c) |
| miR-1269b | PTEN | Down | Zhao et al. (2020b) |
| miR-9-5p | EIF5A2 | Down | Li et al. (2016b) |
| miR-103 | NOR1 | Down | Li et al. (2021c) |
| miR-33a-5p | Not reported | Down | Li et al. (2021c) |
| miR-155-5p | PDK1 | Down | Li et al. (2021c) |
| miR-340-5p | NRF2 | Down | Li et al. (2021c) |
| miR-326 | RUNX2 | Down | Zhao et al. (2020b) |
| miR-31-5p | MAGEA3 | Down | Zhao et al. (2020b) |
| miR-33a-5p | Not reported | Down | Zhao et al. (2020b) |
| miR-4443 | METTL3 | Up | Yang et al. (2020a) |
| miR-32 | SIRT1 | Down | Sun et al. (2017) |
| miR-548a | ROBO1 | Down | Sun et al. (2017) |
| miR-32 and miR-548a levels, leading to an enhanced ROBO1 expression and displaying a DDP-resistant phenotype in A-549 lung cancer cells, thus sensitizing cells to DDP (Zhao et al., 2014). Roundabout guidance receptor 1 (ROBO1), a cancer-promoting gene, has been negatively correlated with the prognosis of patients. ROBO1 promotes the growth and proliferation of tumor-derived cells in DDP-resistant A-549/DDP cells (Yang et al., 2014). ROBO1 expression is inhibited in Hep 3B2.1-7/DDP & MHCC97-L/DDP cells by miR-32 and miR-548a (Meng et al., 2017). ROBO1 expression is increased in Hep3B2.1-7/DDP & Huh-7/DDP Down Li et al. (2019a). ROBO1 expression is decreased in Hep 3B2.1-7/DDP & Huh-7/DDP Down Li et al. (2019a), in Hep3B2.1-7/DDP & Huh-7/DDP Down Li et al. (2019a), in A-549/DDP & NCI-H460 cells Down Pang et al. (2020), in A-549/DDP cells Down Li et al. (2021c), in SMMC-7721/DDP, HuH7/DDP and Hep-G2/DDP cells Down Wu et al. (2019), in A-549/DDP cells42 Down Sun et al. (2017), in PC-9, Calu-3, A-549 & HCC827 cells Down Wei et al. (2020), in A-549/DDP & NCI-H460/DDP cells Down Pang et al. (2020), in A-549/DDP cells Up Song et al. (2021), in A-549/DDP & NCI-H460 cells Down Pang et al. (2020), in A-549/DDP cells Down Li et al. (2021c), in A-549/DDP, NCI-H1299/DDP & Calu-6/DDP cells Down Zhao et al. (2020b), in A-549/DDP cells42 Down Sun et al. (2017).
| miR   | Target                  | Model                        | Expression | References                      |
|-------|-------------------------|------------------------------|------------|---------------------------------|
| miR-21 | PI3K, Akt, mTOR         | in vitro: AGS/DDP            | Up         | Gu et al. (2020)                |
|       | PI3K/Akt                | in vitro: MGC-803 cells      | Up         | Zheng et al. (2017)             |
|       | Not reported            | in vivo: 67 samples of gastric cancer patients | Up         | Qi et al. (2017)                |
| miR-25 | PTEN                    | in vitro: SGC-7901/DDP cells | Up         | Yang et al. (2013)              |
| miR-30a | FOXO3a                 | in vitro: SGC-7901/DDP cells | Up         | He et al. (2017)                |
| miR-34a | LC3-I, LC3-II         | in vitro: SGC-7901 & SGC-7901/DDP cells | Down       | Du et al. (2018)                |
| miR-34c | ABCB1, ABCCC1, ABCG2   | in vitro: SGC-7901/DDP & MGC-803/DDP cells | Down       | Zheng et al. (2018)             |
|        | E2F1                    | in vitro: SGC-7901 cells     | Down       | Zheng et al. (2020)             |
| miR-95-3p | EMP1                   | in vitro: SGC-7901/DDP & AGS/DDP cells | Up         | Ni et al. (2021)                |
| miR-99a-5p | MTMR3                  | in vitro: BGC-823/DDP & SGC-7901/DDP cells | Down       | Sun et al. (2020a)              |
| miR-106a | PTK7                   | in vitro: SGC-7901 & SGC-7901/DDP cells | Up         | Fang et al. (2019)              |
| miR-122 | ERCC1                  | in vitro: MKN74 cells        | Down       | Song et al. (2019)              |
| miR-126 | VEGFA, PIK3R2          | in vitro: SGC-7901/DDP & BGC-823/DDP cells | Down       | Yan et al. (2016)               |
| miR-129 | P-gp                   | in vitro: BGC-823/DDP & MKN45/DDP cells | Down       | Lu et al. (2017)                |
| miR-138 | FOXC1                  | in vitro: NCI-N87/DDP & AGS/DDP cells | Down       | Sun et al. (2021b)              |
| miR-138-5p | ERCC1, ERCC4        | in vitro: SGC-7901/DDP cells | Down       | Ning et al. (2019)              |
| miR-142-3p | ROCCK2                | in vitro: AGS, SGC-7901, MKN45 & BGC-823 cells | Up         | Peng et al. (2020)              |
| miR-144-3p | UBE2D1                | in vitro: AGS/DDP & MKN45/DDP cells | Down       | Li et al. (2021b)               |
| miR-182-5p | Not reported         | in vitro: SGC-7901/DDP & BGC-823/DDP cells | Down       | Huang XX. et al. (2020)         |
| miR-187 | TGF-β/p-SMAD4          | in vitro: SGC-7901/DDP cells | Down       | Zhu et al. (2019)               |
| miR-192-5p | ERCC3, ERCC4        | in vitro: SGC-7901/DDP cells | Down       | Xie et al. (2019)               |
| miR-198 | PIK3R1                 | in vitro: SGC-7901 & BGC-823/DDP cells | Down       | Huang Z. et al. (2019)          |
| miR-200c | ZEB2                   | in vitro: SGC-7901/DDP cells | Down       | Jiang et al. (2017b)            |
| miR-216a-5p | Bcl-2                | in vitro: SGC-7901/DDP cells | Down       | Zhao et al. (2020a)             |
| miR-299-3p | EndoPD1               | in vitro: SGC-7901/DDP cells | Down       | Yang et al. (2020b)             |
| miR-325-3p | GITR                   | in vitro: MKN45 & AGS cells  | Down       | Sun et al. (2020b)              |
| miR-362 | CYLD, NF-κB           | in vitro: SGC-7901, BGC-823, HGC-27, MKN28 & MGC-803 cells | Up         | Xia et al. (2014)               |
| miR-362-5p | SUZ12                 | in vitro: SGC-7901/DDP cells | Down       | Wei et al. (2019)               |
| miR-363 | FBW7                   | in vitro: MGC-803 & HGC-27 cells | Down       | Zhang et al. (2016)             |
| miR-372 | FOXO3a                 | in vitro: MGC-803/DDP & MKN28/DDP cells | Up         | Wang et al. (2020a)             |
| miR-421 | E-cadherin, caspase-3  | in vitro: AGS, MKN28, MKN45, NCI-N87, HGC-27, SNU-16 & SGC-7901 cells | Up         | Ge et al. (2016)                |
| miR-490-3p | HMGA2                 | in vitro: BGC-823/DDP & SGC-7901/DDP cells | Down       | Xia et al. (2021)               |
| miR-497-5p | ATG14                 | in vitro: BGC-823/DDP & SGC-7901/DDP | Down       | Song et al. (2020)              |
| miR-503 | E2F2                   | in vitro: SGC-7901, MKN45, BGC-823, HGC-27, MFC & SGC-7910/DDP cells | Down       | Jiang et al. (2020)             |
| miR-505 | CYLD                   | in vitro: BGC-823/DDP & SGC-7910/DDP cells | Up         | Wang et al. (2020d)             |
| miR-513a-3p | CYP1B1                | in vitro: AGS & NCI-N87 cells | Down       | Cheng et al. (2021)             |
| miR-574-3p | ZEB1                   | in vitro: SGC-7901/DDP cells | Down       | Wang et al. (2019b)             |
| miR-618 | Bcl-2                  | in vitro: BGC-823/DDP & SGC-7901/DDP cells | Down       | Zhang et al. (2020a)            |
| miR-876-3p | TMED3                 | in vitro: SGC-7901/DDP & MKN45/DDP cells | Down       | Peng et al. (2019)              |
| miR-3619-5p | TBL1XR1              | in vitro: AGS/DDP & NUGC-3/DDP cells | Down       | Wu et al. (2020a)               |

TABLE 3 | MicroRNAs involved in DDP-chemoresistance of stomach cancer.
Mechanistically, TNKS2 is targeted by miR-490-3p, and its increased expression promoted the chemoresistance of colorectal cancer cells (Li J. et al., 2021).

Likewise, levels of miR-103 are upregulated hepatocellular carcinoma cells (Luo et al., 2019), while miR-200a is reduced in DDP-resistant lung cancer cells (Tang et al., 2020). Also, NOR1 was targeted by miR-103 (Luo et al., 2019). It has been demonstrated that NOR1, a tumor suppressor gene, is downregulated in NPC cells and NOR1 that enhances cancer stem-like cell properties in tumor cells by enhancing the Akt and Wnt/β-catenin pathways (Wang et al., 2017). Additionally, miR-200a targeted β-catenin, regulating negatively its expression and its downstream molecules cyclin D1 and vimentin (Tang et al., 2020). Furthermore, cyclin D1 is also directly targeted by miR-593-5p in colorectal cancer cells (Qu et al., 2020) and by miR-1296 in breast cancer cells (Albakr et al., 2021). Cyclin D1 levels must be high during G1 phase for a cell to begin DNA synthesis, but then must be reduced to low levels during S phase to allow for efficient DNA synthesis, however, an aberrant cyclin D1 activity is observed in tumor cells (Montalto and De Amicis, 2020). Additionally, enhanced cyclin D1 and surviving expression enhance resistance by reducing G1 phase arrest and apoptosis, downregulating REV3L expression and leading to enhanced cell proliferation and invasive capacity (Zhu et al., 2016). Moreover, REV3L was targeted by miR-29a and miR-4458 and high expression was observed in tumoral tissues due to a decreased expression in lung cancer cells (Chen X. et al., 2019; Pang et al., 2020). However, overexpression of miR-29a could reduce viability and proliferation and enhance DDP-induced apoptosis of A-549/DDP cells treated with 5 μg/ml DDP (Chen X. et al., 2019).

Expression of miR-203 is enhanced in breast cancer cells, and, mechanistically, miR-203 targeted SOCS3, enhancing DDP-resistance (Ru et al., 2011). However, silencing of miR-203 sensitized breast cancer cells, and it was observed that those cells displayed a higher level of p21, associating these changes

### TABLE 4 | MicroRNAs involved in DDP-chemoresistance of breast cancer.

| miR    | Target | Model   | Expression | References                  |
|--------|--------|---------|------------|----------------------------|
| miR-133a | FTL    | in vitro: MCF-7/DDP cells | Down | Chekhun et al. (2013) |
| miR-141-3p | KLF12  | in vitro: MCF-7 & MDA-MB-231 cells | Up | Zhou et al. (2021) |
| miR-199b-5p | PTN    | in vitro: MDA-MB-231, Hs 5767, HCC 1806, HCC1599 & CAL-51 cells | Down | Du et al. (2020) |
| miR-203   | SOCS3  | in vitro: MCF-7, ZR-75 & MDA-MB-231 cells | Up | Ru et al. (2011) |
| miR-218   | BRCA1  | in vitro: MCF-7 & MCF-7/DDP cells | Down | He et al. (2015) |
| miR-381   | MDR1   | in vitro: MCF-7/DDP & MDA-MB-231/DDP cells | Down | Yi et al. (2019) |
| miR-1307  | MDM4   | in vitro: MCF-7/DDP and MDA-MB-468/DDP cells | Down | Wang and Zhu, (2018) |

### TABLE 5 | MicroRNAs involved in DDP-chemoresistance of colorectal cancer.

| miR    | Target | Model   | Expression | References                  |
|--------|--------|---------|------------|----------------------------|
| miR-125b-5p | HK2    | in vitro: HT29, SW820, HCT 116, SW480 & DLD-1 cells | Down | Shi et al. (2020) |
| miR-137 | Not reported | in vitro: SW480, HT-29, SW620 and LoVo cells | Down | Zheng et al. (2021a) |
| miR-148a | WNT10b | in vitro: SW480/DDP cells | Up | Shi et al. (2019) |
| miR-155 | FOXC3  | in vitro: SW620 cells | Up | Gao et al. (2018) |
| miR-487a-3p | SOX9 | in vitro: Samples from patients with colorectal cancer | Up | Sun et al. (2020c) |
| miR-490-3p | TNKS2 | in vitro: MCF-7/DDP, DLD-1, SW480, HCT 116 cells | Down | Li et al. (2021a) |
| miR-497 | Bcl-2  | in vitro: Samples of 162 colorectal cancer patients | Down | Zheng et al. (2021c) |
| miR-526b-3p | IGF1-R | in vitro: HCT 116, LoVo, COLO 205, SW480 & SW620 cells | Down | Guo et al. (2013) |
| miR-593-5p | KLF12  | in vitro: HCT 116/DDP and LoVo/DDP/DDP cells | Down | Zhang et al. (2021) |
| miR-645 | CCND1  | in vitro: Colorectal cancer tissue obtained from 37 patients | Down | Guo et al. (2020) |
| miR-4486 | SOX30  | in vitro: Colorectal cancer tissue | Up | Guo et al. (2017) |
| miR-4486 | ATG7   | in vitro: HCT 116/DDP & SW480/DDP cells | Down | Wang et al. (2021c) |
with decreased chemoresistance (Ru et al., 2011). This is important, due to p21 being a type of cell cycle regulator that plays a dual role in tumor cells, regulating the cell cycle, inducing apoptosis, and inhibiting cell proliferation (Wang L. et al., 2021). MDMs are nuclear factors that regulate the cell cycle at the G1/S phase transition, whose function and expression are altered in various types of human neoplasms (Momand et al., 1998). Degradation of p21 could be mediated by MDM4, in cooperation with MDM2, leading to abrogation of G1 cell cycle arrest (Jin et al., 2008). It has been reported that miR-1307 and miR-127-3p are downregulated in DDP-resistant breast cancer and lung cancer cell, respectively, and, mechanistically, they directly targeted MDM4 and MDM2, promoting DDP-resistance (Wang and Zhu, 2018; Zeng et al., 2020).

3.2 MicroRNAs involved in Autophagy

Autophagy is an intracellular self-digesting process for the regulation of cell homeostasis, that occurs under several stressful conditions, including organelle damage, the presence of abnormal proteins, and nutrient deprivation (Yun and Lee, 2018). In addition, autophagy regulates the properties of cancer stem-cells by contributing to the maintenance of stemness and the development of resistance to anticancer reagents (Yun and Lee, 2018). MiRs are involved in DDP response of tumor cells by regulation of autophagy.

A key initial event in autophagy is the formation of the autophagosome, and this step is mediated by the serine/threonine protein kinase ULK1 (Zachari and Ganley, 2017). Mechanistically, ULK1 is targeted by miR-514a-3p in NSCLC cells (Shen Q. et al., 2020). Moreover, miR-514a-3p was markedly downregulated in lung tissues and cells, and autophagy was found to be promoted (Shen Q. et al., 2020).

Autophagy-related (ATG) genes are indispensable for autophagosome formation, and enhanced autophagy and proliferation, and reduced apoptosis have been related to enhanced ATGs expression in cancer cells (Wang Q. et al., 2021). In this context, miR-17, miR-138-5p and miR-1236-3p enhances autophagy activity in lung cancer cells via ATG7 targeting (Huang FX. et al., 2019; Pan et al., 2019; Wang et al., 2020c). In addition, miR-4486 also enhances autophagy by targeting ATG7 in colorectal carcinoma cells (Wang W. et al., 2021). ATG3 is another key gene involved in autophagy and it is targeted by miR-1 in NSCLC cells (Hua et al., 2018). It has been observed that there was significant miR-1, miR-17, miR-138-5p and miR-1236-3p downregulation in NSCLC cells (Hua et al., 2018; Huang FX. et al., 2019; Pan et al., 2019; Wang et al., 2020c). Likewise, miR-4486 was also decreased in colorectal cancer cells (Wang W. et al., 2021). Moreover, miR-4443 is also upregulated in lung cancer cells. Besides, METTL3 was confirmed as a direct target gene of miR-4443 (Song et al., 2021). METTL3, a m6A methyltransferase, is able to regulate autophagy by increasing the critical genes, such as ATG5 and ATG7 (Liu S. et al., 2020). In this way, enhanced ATG7 levels promote the conversion of LC3-I into LC3-II and improve Beclin-1 expression, supporting autophagy and chemoresistance of lung cancer (Huang FX. et al., 2019; Wang et al., 2020c) and colorectal cancer cells (Wang W. et al., 2021). Beclin-1 also plays an important role in autophagy-induced tumorigenesis and drug resistance, altering cell growth, cellular microenvironment and cell division (Usman et al., 2021). Beclin-1 has been reported to be targeted by miR-30a in liver cancer cells (Zou et al., 2012) and by miR-216b in lung cancer cells (Chen L. et al., 2019), and both miRs are downregulated in both cancer types, suggesting their role in autophagy activity.

Moreover, miR-99a-5p was found to be upregulated in DDP-resistant gastric cancer cells (Sun G. et al., 2020). Mechanistically, miR-99a-5p targeted MTMR3 and enhanced MTMR expression (Taguchi-Atarashi et al., 2010), promoting resistance to chemotherapy in tumors.

3.3 MicroRNAs Involved in Epithelial-to-Mesenchymal Transition

The initiation of metastasis involves an increase in cell motility mediated by loss of cell-cell adhesion, caused by E-cadherin repression and augmented N-cadherin expression, in a process commonly known as epithelial-to-mesenchymal transition (EMT) (Taylor et al., 2010). In this way, high invasive potential, decreased E-cadherin expression and increased DDP-resistance has been found in lung NCI-H1299, H596 and NCI-H522 cancer cells, due to a reduced miR-200c expression (Ceppi et al., 2010), and in liver Hep-G2 and HuH-7 cancer cells, also due to a decreased miR-31-5p expression (Chen et al., 2020).

A molecule implicated in the EMT process is polycomb ring finger (BM1). Enhanced BM1 expression, a known proto-oncogene, promoted EMT, augmented stemness and rendered cell drug resistance (Paranjape et al., 2014). On this basis, it has been reported that miR-802 expression is downregulated in DDP-resistant gastric cancer tissues and cells. Mechanistically, miR-802 directly targeted BM1 and their boosted levels in gastric cancer cells promote EMT process (Liu et al., 2020).

Zinc finger E-box binding homeobox 1 and 2 (ZEB1 and ZEB2) are transcription factors that promote tumor invasion and metastasis by inducing EMT in carcinoma cells (Zhang P. et al., 2015; DaSilva-Arnold et al., 2019). Also, ZEB1 has been found to be targeted by miR-574-3p (Wang M. et al., 2019), while ZEB2 is targeted by miR-200c in gastric cancer cells (Jiang T. et al., 2017) and their upregulation contributed to DDP-resistance. Both miRs were founded to be downregulated in SGC-7901/ DDP cells (Jiang T. et al., 2017; Wang M. et al., 2019). Even more, miR-223, miR-363 and miR-500a-3p directly targeted F-box and WD repeat domain containing 7 (FBXW7) and promote DDP-resistance in gastric cancer cells (Zhang et al., 2016; Wang et al., 2020b; Lin et al., 2020). FBXW7 (also known as FBW7) directly binds and degrades the EMT-inducing transcription factor ZEB2 in a phosphorylation-dependent manner and its loss can induce an EMT phenotype (Li N. et al., 2019). However, since miR-363 and miR-500a-3p are upregulated in gastric cancer MGC-803 and HGC-27 cells, and miR-223 in lung cancer A-549, NCI-H358 and NCI-H1299 cells, those cell lines display an EMT phenotype (Zhang et al., 2016; Wang et al., 2020b; Lin et al., 2020).

Another molecule that participated in the EMT process is doublecortin-like kinase 1 (DCLK1), a cancer stem cell marker.
DCLK1 is functionally involved in maintaining cancer stemness and the process of EMT (Chandrakesan et al., 2016). Also, DCLK1 has been found to be targeted by miR-330-5p and its upregulation contributes to DDP-resistance. Likewise, miR-330-5p was found to be downregulated in lung cancer A-549 and NCI-H1299 resistant cells, promoting DDP-resistance in lung cancer cells (Ge et al., 2021).

Melanoma-associated antigen A3 (MAGEA3) enhances migration, invasion and proliferation by activation of EMT and Wnt signaling pathway in HeLa cells (Gao et al., 2020). In the same way, enhanced expression of MAGEA3 was found in drug-resistant cells (Bertram et al., 1998) and knockdown of MAGEA3 expression caused a reduction in proliferation and colony formation ability (Xie et al., 2016). Mechanistically, MAGEA3 is targeted by miR-31-5p, and its upregulation is associated with DDP-resistance. Likewise, miR-31-5p was found to be downregulated in liver Hep-G2 and Huh-7 cancer cells, thus promoting DDP-resistance (Chen et al., 2020).

Collagen 1A1 (COL1A1) has been highly expressed and associated with poor prognosis in multiple cancers and positively correlated with the abundance of CAFs, macrophages, and tumor-infiltrating lymphocytes, and activation of EMT process (Liu et al., 2021). Also, miR-29b-3p directly target COL1A1 to promote DDP-resistance. Parallel that, it has been reported miR-29a-3p expression was reduced in lung A-549 cancer resistant cells, and augmented COL1A1 levels are associated with DDP-resistance (Jia and Wang, 2020).

Six homeobox 1 (SIX1) and Notch receptor 2 (NOTCH2) protein expressions have been associated with invasive lung cancer, by inducing EMT and thus promoting advanced malignant phenotypes (Minna et al., 2012). Expression of miR-186-5p was downregulated lung A-549/DDP and NCI-H1299 resistant cancer cells. In addition, miR-186-5p negatively regulated SIX1 and SIX1 was upregulated in DDP resistant cancer cells (Liu X. et al., 2020).

SRY-related high mobility group-box 9 (SOX9) is a transcription factor, which acts as a proto-oncogene, implicated with the Wnt/β-catenin pathway activation and in the expression of EMT-associated proteins (Huang JQ, et al., 2019; Panda et al., 2021). Mechanistically, SOX9 is targeted by miR-487a-3p in colorectal cancer cells. Additionally, colorectal cancer cells showed low miR-487a-3p levels, promoting SOX9 expression in colorectal HT29 and SW480 cells, exhibiting the DDP-resistant phenotype (Sun Y. et al., 2020).

Paxillin (PXN) is a cytoplasmatic protein which regulates focal adhesion. Also, PXN has been shown to promote the activation of ERK and enhance the EMT process (Wen et al., 2020). Bioinformatic analysis has proved that PXN is a direct target of miR-199b-5p. Also, decreased miR-199b-5p levels are observed in breast cancer cells, promoting the EMT process by reducing E-cadherin levels (Du et al., 2020). Loss of E-cadherin has been shown to promote the growth, invasion, and enhance drug resistance of CrC cells and, contribute to the progression and metastatic dissemination (Chen et al., 2012).

EIF5A2 plays an important role in many biological processes, including tumor formation, cancer cell growth, maintenance of cancer stem cells and EMT process (Meng et al., 2019). Bao et al. (2020) demonstrated EIF5A2 was targeted by miR-9 and was upregulated in lung tumor cells, thus promoting chemoresistance to DDP by increasing EMT process. Also, Wnt10b has been involved in enhanced tumor cell stemness by upregulation of OCT4 and NANOG expression. In colorectal cancer, WNT10b is directly targeted by miR-148a and the reduced miR-148a expression enhances Wnt10b levels to allow drug resistance in cancer therapy (Shi et al., 2019).

### 3.4 MicroRNAs Involved in Apoptosis

Apoptosis is a form of programmed cell death. In this pathway, molecular mechanisms which trigger inhibition of apoptosis responsible for DDP-resistance includes MAPK dysregulation, enhanced Bcl-2 or Bcl-XL expression, suppression of caspase-3 activity, enhanced PI3K/Akt activity, and so on (Siddik, 2003). A number of miRs have been described to be involved in the regulation of apoptosis.

Mitogen-activating protein kinases (MAPK) are molecules involved in apoptosis. There are three major MAPK pathways that involve the extracellular signal-regulated kinases: ERK1/2, JNK and p38 kinase. Chen et al., proved that MAPK3 was directly targeted by miR-206 in gastric cancer cells (Chen Z. et al., 2019). Also, Sun T. et al. (2020) demonstrated that miR-325-3p interacted with GITR, and upregulated expression contributes to DDP-resistance in gastric cancer cells. On this basis, GITR is able to enhance ERK phosphorylation, suggesting that GITR is associated with MAPK-pathway activation (Ronchetti et al., 2004). Also, Rao et al. (2019) showed that miR-219a-5p directly targeted FGF9, and its enhanced expression leads to DDP-resistance in lung cancer cells. In this way, the low miR-325-3p and miR-219a-5p expression observed in gastric and lung cancer cells activate MAPK pathway, contributing to DDP-resistance (Ronchetti et al., 2004; Rao et al., 2019). Also, Zhou and Chen demonstrated that miR-135b interacted with MST1, and upregulated expression activates MAPK pathway, contributing to DDP-resistant phenotype (Zhou and Chen, 2019).

The intrinsic-mediated apoptotic pathway causes mitochondrial membrane potential loss, cytochrome c release and cleaved caspase-3. Bcl-2 is located in the mitochondrial membrane, and is related to the mitochondrial membrane potential loss and the cytochrome c release (Chen et al., 2015). MiR-7, miR-145, miR-146a, miR-152, miR-181b, miR-200b, miR-200c, miR-429, miR-451, miR-497 and miR-630 are reported to target Bcl-2 in lung cancer tissues and/or cells, and negatively regulate its expression (Zhu et al., 2010; Bian et al., 2011; Zhu et al., 2012a; Zhu et al., 2012b; Cheng et al., 2017; Pang et al., 2017; Chen et al., 2018; Zhang et al., 2019; Zhao et al., 2019). Likewise, miR-497 also interacts with Bcl-2 in colorectal cancer cells (Zheng ZH. et al., 2020). In this way, the low miR-7, miR-152, miR-181b, miR-200b, miR-200c, miR-429, miR-497 and miR-630 expression shown leads to decreased apoptosis incidence, resulting in a DDP-resistant phenotype in lung and colorectal cancer cells. Also, increased Bcl-2 levels have been associated with decreased cleaved-caspase 3 and E-cadherin levels, triggering EMT process and promoting DDP-phenotype (Du et al., 2020). The E2F family consists of 8 genes and 10
protein products encoded by these genes, which are crucial for regulating apoptosis, and they have been classified as transcriptional activators (E2F1-3), predicted to be oncogenic, or transcriptional repressors (E2F4-8), predicted to have tumor suppressor functions (Xie et al., 2021). E2Fs have been associated with the upregulation of Bcl-2, which contributes to uncontrolled tumor growth (Donzelli et al., 2012; Zheng et al., 2020; Zhou, 2020; Wu et al., 2021). In this context, miR-432 and miR-503 suppress E2F3 (Chen L. et al., 2016; Zhou, 2020), miR-34c targets E2F1 (Zheng et al., 2020), and miR-128-2 interacts with E2F5 (Donzelli et al., 2012), by targeting their 3’UTR mRNA. The reduced miR-432 and miR-34c expression observed in lung and gastric cancer cells were associated with advanced tumor stage and mortality and allowed E2F1 and E2F3 to be overexpressed in DDP-resistant phenotype (Chen L. et al., 2016; Zheng et al., 2020). Another molecule implicated in apoptosis is ID1. ID1 regulates p53 and NF-kB pathways, regulating Bax and Bcl-2 genes, thus providing a survival advantage under drug treatment (Kim et al., 2008). In this sense, miR-381 directly targeted ID1 and the reduced miR-381 levels observed in lung cancer cells allows an enhanced ID1 expression, reducing apoptosis and triggering a DDP-resistant phenotype (Huang et al., 2018). Finally, JNK2 negatively regulates the activity of genes related to tumor suppression and the induction of cell apoptosis (Chen et al., 2002). Regarding that, JNK2 was identified as a direct target of miR-146a and the low miR-146a levels reduced the apoptosis rate and enhanced the relative invasion rate of lung cancer cells (Pang et al., 2017).

The PI3K-Akt pathway is a major survival pathway activated in cancer. In this sense, phosphatase and tensin homolog (PTEN) is a molecule capable of inactivating the Akt signaling pathway and acts as a negative regulator of PI3K/Akt signaling (Georgescu, 2010). Also, PTEN/PI3K/Akt pathway regulates the signaling of multiple biological processes, such as apoptosis, and also enhances PI3K/Akt/mTOR pathway, conferring drug resistance and further cancer progression in breast cancer cells (Dong et al., 2021). MiR-18a, miR-19a, miR-21, miR-25-3p, miR-130b and miR-1269b in lung cancer cells (Xiao et al., 2018; Zhang et al., 2018; Xing et al., 2019; Yang et al., 2020; Gu et al., 2020; Sun B. et al., 2021; Liang et al., 2021), and miR-21 and miR-106a in gastric cancer cells (Fang et al., 2013; Yang et al., 2013; Zheng et al., 2017) directly regulate PTEN, and reduced miRs levels expression in cancer cells promote PTEN expression, triggering apoptosis and DDP-resistance. Additionally, HMGAA2 and KLF4 regulation are able to promote PI3K/Akt phosphorylation, resulting in increased drug resistance (Deng et al., 2021), and miR-26a interacts with HMGAA2 (Yang et al., 2016) and miR-145 with KLF4 (Cui et al., 2018) to promote DDP-resistance in lung cancer cells. Moreover, MET, a proto-oncogene, also activates PI3K/Akt pathway via promoting PTEN and CDKN1A expression and reducing apoptosis (Ohta et al., 2015). In this way, miR-206 regulates MET protein in A-549 lung cancer cells by directly targeting MET 3’-UTR and activated MET/PI3K/Akt/mTOR signaling pathway to induce DDP resistance (Chen QY. et al., 2016). To contribute to Akt activation and DDP-resistance, PI3K also is targeted by miR-10a (Huang T. et al., 2020). In the same way, two downstream effectors of the PI3K/Akt pathway are also regulated by miRs. Mammalian target of rapamycin (mTOR) acts as a target gene of miR-100-5p in lung cancer (Qin et al., 2017) controlling cell growth, proliferation and survival (Populo et al., 2012). Besides, FOXO3 also is regulated by miR-155 in colorectal cancer cells (Gao et al., 2018) and by miR-372 in gastric cancer cells (Wang C. et al., 2020), and enhanced FOXO3 expression by Akt promotes cell survival and resistance (Populo et al., 2012). Even more, miR-155-5p also targets PDK1 in liver cancer (Li et al., 2021c). It has been shown that PDK1 and PDK2 cause phosphorylation and activation of Akt after its translocation to inner membrane, modulating the function of numerous substrates involved in the regulation of cell survival, cell cycle progression and cellular growth (Fresno Vara et al., 2004). So, enhanced expression of miR-155-5p increases cell proliferation and reduces apoptosis of Hep3B2.1-7 liver cancer cells (Li et al., 2021c).

Other signal transductions involved in DDP-resistance are the nuclear factor (NF)-κB and apoptosis-related signaling pathways. NF-κB is known to play an important role in cell survival and inflammation. Several miRs have been reported to regulate NF-κB, such as miR-146a, miR-152 and miR-381 in lung cancer cells (Jiang P. et al., 2017; Huang et al., 2018; Zhao et al., 2019). Reduced expression of miR-146a (Jiang P. et al., 2017), miR-152 (Zhao et al., 2019) and miR-381 (Huang et al., 2018) is observed in DDP-resistant A-549 cells, which gives rise to a heightened NF-κB expression and promotes DDP-resistant phenotype. Moreover, another study demonstrated that GSTP1 was able to interact with IKKβ to activate NF-κB and induced the expression and release of IL-6, thus mediating drug resistance in breast cancer cells (Dong et al., 2020). Furthermore, miR-133b was diminished in DDP-resistant lung cells (Lin et al., 2018). Finally, miR-362 and miR-505 overexpression were observed in gastric cancer cells (Xia et al., 2014; Wang Z. et al., 2020), and their enhanced expression promoted nuclear accumulation of NF-κB/p65, due to both miRs targeted CYLD directly and its downregulation mediated NF-κB activation. Besides, Zhang and Luo found that miR-29c was downregulated in HepG2/DDP cells, and demonstrated that miR-29c targeted SIRT1 (Zhang and Luo, 2018). SIRT1 may have enhanced activity in tumor cell growth by promoting NF-κB expression (Yeung et al., 2004).

The Wnt/β-catenin signaling pathway participates in various physiological processes such as proliferation, differentiation, apoptosis, migration and invasion; on the other hand, dysregulation of the Wnt/β-catenin contributes to the development and progression of some solid tumors (Ge and Wang, 2010). Mir-130b, miR-140-3p, miR-326, and miR-1249 directly enhance the noncanonical Wnt pathway in liver and lung cancer cells (Zhang et al., 2018; Wu S. et al., 2020; Carotenuto et al., 2020; Wu Y. et al., 2020). Also, SOX30, a tumor suppressor, acts as a transcription factor by binding directly to the p53 promoter and reduces SOX30 expression, resulting in enhanced β-catenin expression and Wnt/β-catenin pathway activation (Liu et al., 2020c). Guo et al. (2017) demonstrated miR-645 directly targeted SOX30 in colorectal cancer cells, enhancing DDP-resistant phenotype.

Other molecules also have been reported to confer DDP-resistance by inhibiting apoptosis. CYP1B1, a cytochrome
P450 enzyme, is overexpressed in malignant ovarian cancer (Zhu et al., 2015). MiR-513a-3p had the same binding site to CYP1B1, low miR-513a-3p levels enhance CYP1B1 expression, conferring DDP-resistance by reducing DDP-induced apoptosis in gastric cancer cells (Cheng et al., 2021). ROCK1 and ROCK2 proteins are narrowly associated with tumor progress and lymph node metastasis (Zhang J. et al., 2015). Moreover, ROCK2 was regulated by miR-142-3p, and its reduced levels enhance ROCK2 expression, resulting in a DDP-resistant phenotype by reducing DDP-induced apoptosis in gastric cancer cells (Peng et al., 2020).

3.5 MicroRNAs Involved in Drug Efflux

The reduced uptake of water-soluble drugs and augmented drug efflux from cancer cells are the biochemical and cytological mechanisms of drug resistance in cancer cells (Chen et al., 2015). P-glycoprotein (P-gp, also known as MDR1) is encoded by the multidrug resistance gene (ABCB1). P-gp acts as a drug pump and it can bind to several drugs and pump them out of the cells, thereby decreasing their intracellular concentration and the sensitivity of cancer cells to the drug (Breier et al., 2005). P-gp is influenced by miR-30 and miR-129 in gastric cancer cells (Lu et al., 2017; Du et al., 2018), and by miR-144-3p, miR-145, and miR-202-5p in lung cancer cells (Tian et al., 2019; Zhang et al., 2019; Shen JG. et al., 2020).

Also, two additional ABC transporters, the multidrug resistance-associated protein 1 (MRP1; encoded by ABCC1), and ABCG2 are also implicated in multidrug resistance (Robey et al., 2018). Mechanistically, ABCC1 was targeted by miR-185-5p and negatively regulates its expression in lung cancer cells (Pei et al., 2016). Additionally, miR-144-3p and miR-145 also influenced the expression of MRP1 in lung cancer cells (Tian et al., 2019; Zhang et al., 2019), and by miR-381 in breast cancer cells (Yi et al., 2019), thus contributing to DDP-resistant phenotype.

4 CONCLUSION AND FUTURE PERSPECTIVES

Resistance to DDP is a major challenge that hampers the success of cancer treatment. According to current knowledge, multiple factors such as DNA damage and repair, transport process, autophagy, and apoptosis are involved in resistance to platinum-based drugs. Some dysregulated miRs functioned as an oncogenic molecules and others acted as a tumor repressor, and we tried to provide a general vision about this effect. Understanding the underlying molecular mechanisms of DDP-resistance is fundamental to reverse chemoresistance. In this way, it is possible to develop strategies to identify biomarkers of drug response and resistance, being useful in future clinical trials and rational management of cancer patients (Figure 2). Vast evidence shows that specific miRs can be regulated and then targets downstream genes to re-sensitize cancer cells to the effects of DDP. For example, lidocaine alleviates DDP-resistance of MGC-803/DDP gastric cancer cells, inhibiting their migration through decreasing miR-10b expression (Zhang X. et al., 2020). Besides, the use nanoliposomes loaded with miR-1296 sensitizes breast cancer cells to DDP, by reducing CCND1, and thus, EMT process (Albakr et al., 2021). Finally, curcumin treatment is able to restrain the proliferation and facilitated apoptosis in HCT8/DDP cells, by promoting miR-497/Bcl-2 axis (Zheng ZH. et al., 2021). Consequently, it is just a matter of time until miR-based therapies be proved to restore the sensitivity of tumor cells to some anticancer drugs including DDP.

In this review, we have summarized some of our current understanding of microRNAs that affect DDP-resistance and some strategies that have been employed to sensitize cancer cells to DDP chemotherapy. These studies have improved our understanding of the involvement of miRs in drug resistance and provide a starting point for the development of ncRNA-based therapy to accelerate the resolution of DDP-resistance in many cancers, to improve the quality of life and prognosis of patients.

AUTHOR CONTRIBUTIONS

PL, NS, and KS contributed to the conception of the summarize, performed the data analyses and wrote the manuscript. NT and MV performed figures and tables. NT, PM, and LS reviewed and edited the manuscript. All authors read and approved the manuscript.

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