

Review

The Role of miRNAs in Regulating Cellular Senescence: A Potential Strategy for Overcoming Drug Resistance in Ovarian Cancer

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Abstract

Ovarian cancer remains one of the most lethal gynecological malignancies, largely due to late diagnosis and the frequent development of resistance to platinum-based chemotherapy and taxanes. Increasing evidence implicates microRNAs as key regulators of drug response through their control of DNA damage response and repair, apoptosis, epithelial–mesenchymal transition, and therapy-induced cellular senescence. Senescence is a double-edged process characterized by irreversible cell-cycle arrest and the secretion of pro-inflammatory factors collectively known as the senescence-associated secretory phenotype, which may suppress tumor growth but also promote chemoresistance and disease recurrence. This review summarizes current evidence on microRNA (miRNA)-mediated regulation of therapy-induced cellular senescence and its role in drug resistance in ovarian cancer. We integrate data from mechanistic studies, preclinical models, and clinical observations, focusing on senescence-associated miRNAs and their regulatory networks. miRNAs including miR-34a, miR-21, miR-146a, miR-200c, miR-506, and miR-433 regulate key senescence pathways, notably p53/p21 and p16-RB signaling, and modulate the senescence-associated secretory phenotype by controlling inflammatory mediators, extracellular matrix remodeling, and angiogenic factors. Several of these miRNAs are also associated with resistance to platinum-based chemotherapy, taxanes, poly ADP-ribose polymerase (PARP) inhibitors, and immunotherapies through effects on PI3K/AKT and Hippo signaling pathways, as well as DNA repair mechanisms. Emerging therapeutic strategies aim to modulate or eliminate senescent cells using miRNA mimics, inhibitors, or gene-editing approaches, including nanoparticle-based delivery systems. Although preclinical studies suggest that these approaches may restore chemosensitivity, clinical translation remains limited by delivery challenges, off-target effects, and the context-dependent role of senescence. Targeting miRNA-senescence regulatory axes may represent a strategy for addressing drug resistance in ovarian cancer and warrants further investigation as part of combination treatment strategies.

Keywords: microRNAs; cellular senescence; ovarian neoplasms; drug resistance; senescence-associated secretory phenotype; cellular microenvironment; microRNAs/therapeutic use

1. Introduction

1.1 Overview of the Clinical Problem of Drug Resistance in Ovarian Cancer

Ovarian cancer remains one of the most deadly gynecological cancers, with a 5-year survival rate of about 45% for all stages of advancement, and in cases diagnosed at a late stage (III–IV), this rate drops to 25%–40% [1,2,3]. Every year worldwide, approximately 314,000 new cases of ovarian cancer are diagnosed, and the number of deaths is around 207,000 [4]. The main problem in treatment is the high frequency of resistance to chemotherapy, especially to platinum drugs, which are the standard in treatment. Resistance to chemotherapy is a major factor influencing therapeutic failures and disease recurrence. It has been shown that about 70% of women with advanced ovarian cancer, who initially respond to platinum-based chemotherapy, develop a recurrence associated with drug resistance within two years [5]. In the context of patients with platinum resistance, responses to standard therapies are only 5%–15%, which drastically reduces the chances of long-term survival [6]. The objective of this comprehensive review is to

summarize current evidence on miRNA-mediated regulation of cellular senescence, elucidate the underlying molecular pathways, and explore how modulating senescence-associated miRNAs can restore chemosensitivity in resistant ovarian cancer.

1.2 Overview of Current Therapeutic Strategies and Their Limitations

Currently used therapies include surgical treatment, chemotherapy with platinum-based drugs and taxanes, and targeted therapies such as poly ADP-ribose polymerase (PARP) inhibitors (Table 1, Ref. [7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35]). Although PARP inhibitors show effectiveness in delaying disease recurrence, their efficacy is limited in cases of chemotherapy resistance, particularly due to DNA repair mechanisms [1,5,6]. In reality, patients with primary resistance to carboplatin and paclitaxel have worse prognoses, including a shorter progression-free survival (PFS) and a lower overall survival (OS) rate [36,37,38]. Mechanisms of drug resistance



in ovarian cancer, as in other neoplastic diseases, are complex and include, among other things, decreased drug accumulation, increased activity of MDR1 (multidrug resistance protein) efflux pumps, changes in signaling pathways regulating apoptosis, and adaptation to cellular stress [1,39,40]. In platinum-resistant patients, intensifying therapy, e.g., increasing the cisplatin dose fivefold, may be an effective approach to enhance drug sensitivity [1,41].

2. MicroRNA as a Regulatory Response to Therapy in Ovarian Cancer

In the context of searching for new therapeutic strategies, increasing attention is being paid to the role of microRNA (miRNA). miRNA, as a short non-coding RNA, regulates genes key to cancer processes such as apoptosis, cell proliferation, and angiogenesis [42]. It is also worth paying attention to the role of these molecules in regulating cellular senescence, whose induction may play an important role in treatment response or in reversing drug resistance.

Biogenesis of miRNA, Mechanism of Action, and Role in Gene Expression Regulation

MicroRNAs (miRNAs) are small, non-coding RNA molecules about 18–25 nucleotides long that play a key role in regulating gene expression at the post-transcriptional level. The biogenesis of miRNA begins in the cell nucleus, where miRNA-encoding genes are transcribed by RNA polymerase II, creating primary miRNA transcripts (pri-miRNA). Then, pri-miRNAs are processed by the Drosha-DGCR8 complex into hairpin-shaped pre-miRNAs, which are exported to the cytoplasm by exportin-5 [43,44,45,46]. In the cytoplasm, the enzyme Dicer converts pre-miRNA into mature miRNA, which forms a complex with Argonaute proteins, thereby forming the RNA-Induced Silencing Complex (RISC). The RISC complex allows the miRNA to bind to the 3' UTR region of the target mRNA, resulting in the inhibition of translation or degradation of the mRNA [45,46,47]. The mechanism of miRNA action mainly involves binding to complementary sequences in the 3' UTR of the target mRNA, leading to its degradation or translational repression.

Owing to their capacity to simultaneously regulate large sets of mRNA transcripts, microRNAs act as molecular hubs integrating complex signaling and adaptive networks [48,49,50]. Under conditions of cellular stress, including oxidative stress and DNA damage, miRNA biogenesis and activity are dynamically reshaped, enabling coordinated adaptive responses that determine cell fate [51,52]. Within the tumor microenvironment, miRNAs critically modulate intercellular communication by regulating angiogenesis, immune surveillance, and inflammatory signalling [48,49,53]. In ovarian cancer, aberrant miRNA expression is well-documented and plays a crucial role in pathogenesis by affecting signaling pathways essential for tumor development [42,47,54]. Selective modulation of miRNAs such

as miR-155 or miR-124 has been shown to reprogram the immune microenvironment and enhance antitumor immune activity [51,55,56]. Conversely, global dysregulation of miRNA networks disrupts senescence-associated programs and facilitates the development of therapy resistance. In this context, miRNAs function at the intersection of redox regulation, DNA damage response, and proliferative signaling, thereby influencing tumor cell proliferation, migration, and sensitivity to anticancer treatment [50,52,57] (Table 2). This context-dependent and pleiotropic mode of action underscores the value of miRNAs as both biomarkers and therapeutic targets. Accordingly, miRNA-based strategies, including the use of miRNA mimics to restore tumor-suppressive functions and antagomiRs to inhibit oncogenic miRNAs, are actively being explored [48,49,51,52,57,58]. The small size of miRNAs and their compatibility with advanced delivery platforms further support their translational potential by enabling tumor-selective delivery with reduced systemic toxicity [49].

3. Drug Resistance Mechanisms in Ovarian Cancer

Ovarian cancer is characterized by a high tendency to develop resistance to the drugs used in its treatment, which poses a key therapeutic challenge. Drug resistance in ovarian cancer is a multifaceted phenomenon that involves a range of molecular and cellular mechanisms affecting the effectiveness of therapy. Key mechanisms include changes in drug metabolism, DNA repair mechanisms, reduced apoptosis, and activation of pro-survival pathways. In particular, resistance to platinum-based drugs and taxanes results from various molecular adaptations that enable tumor survival (Table 1).

One of the main mechanisms of resistance to chemotherapy in ovarian cancer is the overexpression of transporters from the ATP-binding cassette (ABC) family, such as ABCB1, also known as P-gp (P-glycoprotein) [59,60,61,62]. ABCB1 actively transports paclitaxel out of the cell, reducing its intracellular concentration and thereby limiting the effectiveness of the therapy [1,63]. In ovarian cancer cells, ABCB1 expression is often elevated, correlating with resistance to chemotherapy [64]. Research has shown that P-gp inhibition restores sensitivity to paclitaxel and olaparib, suggesting the potential use of a combination of these drugs in therapy [1,7].

Inhibition of apoptosis is another important resistance mechanism. In ovarian cancer, tumor cells increase the expression of anti-apoptotic proteins from the Bcl-2 family, such as Bcl-XL and Mcl-1, which inhibit drug-induced cell death [1,65]. Paclitaxel can convert the Bcl-2 protein into a pro-apoptotic form, but this is compensated for by the overexpression of other anti-apoptotic proteins, which ultimately leads to resistance [66]. Changes in the activation of the PI3K/AKT pathway also promote cell survival, which contributes to resistance [67]. In the case of platinum-based

Table 1. miRNAs associated with drug resistance in ovarian cancer.

Drug group	Specific drugs	miRNA markers		Resistance mechanisms	Citations
Platinum compounds	Cisplatin, Carboplatin	miR-205-5p, miR-216a, miR-224-5p, miR-149-5p, miR-493-5p, miR-98-5p, miR-20a	miR-483-3p, miR-30b, miR-1180, miR-31, miR-551b	PTEN/AKT Pathway Inhibition: miR-205-5p and miR-216a decrease PTEN activity, boosting resistance. PRKC Silencing: miR-483-3p and miR-224-5p silence PRKC family members, reducing cell death. Hippo Pathway Downregulation: miR-30b and miR-149-5p target genes like MST1, affecting growth control. Suppression of Tumor Suppressors: miR-551b downregulates FOXO3 and TRIM-31, associated with worse survival.	[8,9,10,11,12,13,14,15,16,17,18,19]
Taxanes	Paclitaxel, Docetaxel	miR-21, miR-1307, miR-215, miR-200c, miR-503-5p, miR-383-5p	miR-630, miR-181a, miR-200b, miR-92, miR-136, miR-874	Apoptosis Suppression: miR-21 and miR-630 inhibit APAF1, reducing PTX-induced apoptosis. CIC/ING5 Downregulation: miR-1307 targets CIC and ING5, lowering PTX sensitivity. EMT Activation: miR-181a increases EMT markers, promoting cell invasion. Bcl-2 Pathway Control: miR-215 silences XIAP, increasing PTX sensitivity.	[20,21,22,23,24,25,26,27,28,29,30]
PARP inhibitors	Olaparib, Rucaparib, Niraparib	miR-493-5p, miR-506-3p	miR-622, miR-200c	Stabilization of Replication Forks: miR-493-5p affects RNASEH2A and FEN1, maintaining DNA replication under stress. HR and NHEJ Modulation: miR-622 rescues HR in BRCA1 mutants, counteracting PARPi effects. EZH2/β-Catenin Suppression: miR-506-3p silences EZH2, enhancing PARPi efficacy.	[7,16,31,32]
Immunotherapy	Pembrolizumab, Nivolumab	miR-155, miR-424	miR-146a	Immune Evasion: miR-155 upregulates PD-L1 expression, reducing immune cell recognition. Enhanced Anti-Tumor Immunity: miR-146a and miR-424 suppress immune checkpoints (e.g., CTLA-4, PD-L1), inhibit immunosuppressive cells, and enhance CD8+ T-cell engagement.	[33,34,35]

PARP, poly ADP-ribose polymerase; miRNA, microRNA; HR, homologous recombination.

therapy, such as cisplatin and carboplatin, a key resistance mechanism is increased DNA repair [68]. The drugs form bonds with DNA, causing damage that triggers repair responses in the cell. In ovarian cancer, the activity of DNA repair pathways, such as nucleotide excision repair (NER) and homologous recombination (HR), is often increased, allowing cells to efficiently repair damage caused by cisplatin [69]. The ERCC1 protein, involved in NER, is often overexpressed in cisplatin-resistant cells, which reduces the effectiveness of treatment [70].

Epigenetic changes, such as DNA methylation and histone modifications, are an important factor in drug resistance in ovarian cancer. For example, hypermethylation of the MLH1 promoter silences the gene and confers cisplatin resistance by disrupting the DNA damage repair response [71]. Other epigenetic changes, such as overexpression of EHMT1/2, can activate DNA repair pathways and enhance resistance to PARP inhibitors [72]. Demethylation of genes encoding ABC transporters may also increase their expression and enhance drug resistance [73,74].

Table 2. Molecular markers and mechanisms of cancer cellular senescence: implications for therapy sensitivity.

Marker category	Senescence marker (gene/pathway)	Mechanism
DNA damage response	<i>p16INK4a</i> , <i>p21CIP1/WAF1</i> , <i>γH2AX</i> , <i>53BP1</i> , <i>ATM</i> , <i>ATR</i>	Cell cycle arrest in response to DNA damage. Activation of DNA repair pathways leads to a permanent halt of the cell in the G1 phase, which is crucial in senescence.
Cell cycle arrest	<i>p16-pRB</i> , <i>p53-p21</i> , <i>Rb-E2F</i> axis, CDK inhibitors	Activation of mechanisms controlling the cell cycle, including the p53-p21 pathway and p16-pRB, leads to cell cycle arrest in the G1 phase, preventing cell division.
Senescence-associated secretory phenotype	<i>IL-6</i> , <i>IL-8</i> , <i>MCP-1</i> , <i>TNF-α</i> , <i>MMPs</i> , <i>VEGF</i>	As a result of senescence, cells secrete pro-inflammatory cytokines and growth factors that influence the tumor microenvironment, inducing an inflammatory state that may support the development of metastases and treatment resistance.
Telomere dysfunction	<i>TERRA</i> , <i>hTERT</i> , Shelterin complex (<i>TRF1</i> , <i>TRF2</i> , <i>RAP1</i>)	Damage to telomeres leads to the activation of repair mechanisms, but in cancer cells, telomeres can still be shortened, which triggers senescence mechanisms.
Mitochondrial dysfunction	<i>PINK1</i> , Parkin, <i>TOMM40</i> , Mitochondrial DNA depletion	Mitochondrial dysfunction associated with the accumulation of mutations in mitochondrial DNA leads to oxidative stress, which is one of the main mechanisms inducing senescence.
Autophagy	<i>LC3B</i> , Beclin-1, <i>ATG5</i> , <i>ATG7</i>	Defects in autophagy, which normally removes damaged organelles and proteins, can lead to the accumulation of toxic substances and cellular stress, promoting senescence.
Senescence-associated heterochromatic foci (SAHF)	H3K9me3, HP1α, Lamin B1	Accumulation of heterochromatin in senescent cells causes the loss of function of genes responsible for cell division, which blocks the possibility of further proliferation.
Inflammatory pathways	<i>NF-κB</i> , <i>NLRP3</i> , <i>STING</i> , inflammasome components	Activation of inflammatory pathways, such as NF-κB and inflammasome, in cancer cells can lead to senescence but also supports a pro-inflammatory microenvironment that promotes tumor progression.
Cellular stress response	<i>HSP70</i> , <i>HSP90</i> , <i>XBPI</i> , <i>ATF4</i> , <i>CHOP</i>	Cell stress, particularly related to improper protein folding or metabolic disturbances, activates cellular responses that can lead to aging.
Tumor suppressor pathways	<i>ARF</i> , <i>PTEN</i> , <i>LKB1</i> , <i>BRCA1/2</i>	Disorders of tumor suppressor gene functions, such as ARF and PTEN, lead to the activation of DNA repair mechanisms and damage responses, which promote cell cycle arrest and senescence.
Epigenetic modifications	DNA methylation of <i>p16INK4a</i> , <i>H3K27me3</i> , <i>H3K9me3</i> , <i>EZH2</i>	Epigenetic changes, such as DNA methylation and histone modifications, can lead to the activation or inactivation of genes related to the cell cycle and senescence.
Reactive oxygen species (ROS)	<i>Nrf2</i> , <i>SOD2</i> , <i>CAT</i> , <i>GPX</i> , <i>NRF1</i> , <i>p38 MAPK</i>	An increase in reactive oxygen species (ROS) levels due to mitochondrial damage or metabolic disturbances leads to the activation of stress responses and senescence.
Cellular senescence and therapy sensitivity	CDK4/6 inhibitors, Senolytics (e.g., Dasatinib, Quercetin), <i>FOXO4-DRI</i>	Therapeutic interventions, such as CDK4/6 inhibition or the use of senolytics, eliminate senescent cells, restoring treatment sensitivity, especially in cancer therapy.

3.1 miRNAs Associated With Drug Resistance in Ovarian Cancer and Their Impact on Signaling Pathways

Resistance to chemotherapy is one of the biggest challenges in ovarian cancer treatment, contributing to the high mortality associated with this tumor [75,76,77]. Many miRNAs play a key role in regulating mechanisms of drug resistance, affecting various signaling pathways and cellular processes. Research on the involvement of miRNAs

in regulating apoptosis has revealed their crucial role in therapeutic response in ovarian cancer, particularly in drug resistance and sensitivity (Table 1). MicroRNAs such as miR-21, miR-214, miR-137, and miR-221/222 play an important role in inhibiting apoptosis by regulating key pro-apoptotic genes like *PTEN*, *BCL-2*, and *XIAP*. In the context of ovarian cancer, miRNAs interact with numerous molecular pathways, influencing cancer cells' ability to in-

duce apoptosis and modulating their response to chemotherapeutic agents, especially cisplatin [78,79,80,81,82]. MiR-137 plays a crucial role in regulating the apoptosis inhibitor (XIAP) by interacting with its 3' UTR region, which is key to cisplatin sensitivity. Experiments conducted using miR-137 showed that its overexpression leads to a decrease in XIAP protein levels, significantly enhancing cisplatin-induced apoptosis, and reducing the resistance of SKOV3 cells and primary EOC cells to this drug [80]. MiR-21 and miR-214 are among the best-studied miRNAs in the context of chemotherapy resistance; their overexpression inhibits *PTEN*, thereby activating the PI3K/AKT pathway and promoting cell survival and resistance to therapy, especially platinum-based treatments [83,84,85,86,87]. MiR-21 affects drug resistance by also regulating the levels of proteins such as PDCD4 and c-IAP2, which respectively promote apoptosis and inhibit apoptosis. Blocking miR-21 has the opposite effect, restoring sensitivity to cisplatin and increasing apoptosis in cancer cells, making it a potential therapeutic target for resistant ovarian cancer [82].

miRNAs also significantly impact cellular autophagy, which can indirectly influence their ability to survive under therapy. Autophagy, regulated by miRNAs, as shown in studies, modulates the expression of genes related to stress response and may serve as an adaptive mechanism for cancer cells, promoting their survival in the presence of drugs. In particular, miRNAs can function as biomarkers for ovarian cancer progression and predictors of therapy response [78]. It has been shown that some miRNAs, by modulating autophagy, can reverse cisplatin resistance in cancer cells [78]. For example, miRNA-20a-5p inhibits autophagy and resistance to cisplatin in ovarian cancer cells by methylating *DNMT3b* and repressing *RBPI*, thereby modulating the sensitivity of ovarian cancer cells to radiotherapy through the regulation of autophagy [78,88]. The expression profile is closely related to the clinical and pathological characteristics of tumors; miRNAs selected in the sequencing study in patients with high-grade ovarian cancer at stage I showed high diagnostic accuracy. Additionally, miRNAs such as miR-30a and miR-204 regulate the autophagy process by modulating the expression of genes like *Beclin-1* and *ATG5*, which promotes treatment resistance [78,89].

The ability of cancer cells to repair DNA damage is a key factor in their resistance to chemotherapy, especially to drugs that induce DNA damage [77]. miRNAs play a crucial role in the DNA damage response (DDR), modulating both the efficiency of DNA repair and the sensitivity of cancer cells to treatment. In ovarian cancer, miR-146 affects the integrity of repair pathways by suppressing *BRCA1*, which reduces the cells' ability to effectively repair double-strand breaks (DSBs) and makes them more susceptible to damage caused by genotoxic therapy [90]. The overexpression of miR-182 and miR-9 constitutes an additional mechanism leading to the silencing of *BRCA1*, which significantly increases ovarian cells' susceptibility to cisplatin-

based chemotherapy and PARP inhibitors (PARPis), which work precisely by damaging DNA and depleting the cells' repair resources [91,92]. In this way, miRNAs can act as molecular 'sensors' in cancer therapy, influencing cellular decisions regarding survival and apoptosis in response to DNA damage.

MiR-96 is another example of an miRNA involved in repair mechanisms, by regulating RAD51 and REV1, key proteins of the homologous recombination (HR) pathway, miR-96 effectively reduces the cells' ability to accurately repair DSBs, which decreases their resistance to PARP inhibitors and other DNA-damaging therapies [93]. Other miRNAs, such as miR-1255b, miR-193b, and miR-148b, target transcripts encoding *BRCA1*, *BRCA2*, and *RAD51*, thereby further weakening the HR pathway in ovarian cancer cells, increasing their susceptibility to PARP inhibitor therapy and reducing their ability to repair DSBs [94]. An interesting group of markers with clinical significance in the context of treatment response are miR-506, miR-103, and miR-107, which act as molecular indicators of chemotherapy effectiveness and patient survival prognosis. By reducing RAD51 activity and inhibiting the formation of repair foci, these miRNAs can enhance DNA damage in cancer cells while simultaneously decreasing their chances of effective recovery after therapy [95,96]. However, prolonged exposure to factors such as cisplatin or PARP inhibitors often leads to the development of resistance mechanisms, including reversion mutations in genes such as *BRCA1/2*, *RAD51C*, and *PALB2*, which partially restore HR function in cancer cells. This is a key adaptive process that allows cancer cells to continue proliferating despite aggressive treatment, indicating the need for further research into the role of miRNA as therapeutic targets in the fight against drug resistance [97].

Another process contributing to the development of treatment resistance is epithelial-mesenchymal transition (EMT). EMT is a process by which cancer cells acquire migratory and invasive abilities, contributing to treatment resistance. MiR-200c regulates EMT by inhibiting the expression of transcription factors ZEB1 and ZEB2, leading to the suppression of cancer cell migration and invasiveness [98,99]. Furthermore, it has been shown that microRNAs from the miR-200 family have the potential to predict the response to treatment in patients with ovarian cancer. It was found that higher levels of miR-200 (miR-141, miR-200a, miR-200b, miR-200c, miR-429) correlate with lower levels of β -tubulin III protein, which is associated with resistance to paclitaxel treatment. Low expression of miR-200 was associated with higher levels of β -tubulin III, poorer treatment response, and worse progression-free survival (PFS) [100]. miR-200c also inhibits EMT by decreasing the expression of integrin β 1 (*ITGB1*), which leads to a reduction in the invasive potential of ovarian cancer cells [101,102]. Meanwhile, miR-29b also targets *ITGB1*, blocking metastasis and invasion of cancer cells, and its overexpression in

ovarian cancer cells inhibits migration and invasion, indicating the therapeutic potential of miR-29b in ovarian cancer treatment [103]. Another miRNA, miR-506, decreases the expression of integrins ITGA6 and ITGB3, which suppresses the progression of ovarian cancer, including cell migration and invasion [104]. Additionally, miR-92a regulates the expression of integrin $\alpha 5$, which plays an important role in the adhesion and spread of ovarian cancer cells, and reducing its level through overexpression of miR-92a in cancer cells inhibits peritoneal dissemination in *in vivo* models [105]. MiR-17, whose expression is negatively correlated with the levels of ITGA5 and ITGB1 in EOC cell lines, reduces cell adhesion and invasion as well as the number of peritoneal metastases *in vivo*, targeting ITGA5 and ITGB1 [106]. These results suggest that miRNA, through its influence on EMT and regulation of integrins, may serve as potential targets in the treatment of therapy resistance related to the EMT process in ovarian cancer.

miRNAs can therefore serve as useful and minimally invasive predictive biomarkers in ovarian cancer, as their abnormal expression often correlates with treatment response. Additionally, the stability of miRNAs in bodily fluids makes them attractive candidates for reliable diagnostic and prognostic biomarkers.

3.2 The Role of Cellular Senescence in Developing Drug Resistance and Its Impact on the Ovarian Cancer Microenvironment: Implications for Therapy and Molecular Mechanisms

Cellular senescence is a process characterized by an irreversible arrest of the cell cycle, often triggered by genotoxic stresses such as DNA damage, oxidative stress, or oncogene expression (Fig. 1). In cancers, including ovarian cancer, cellular senescence is a key mechanism that limits the proliferation of cancer cells and influences their response to treatment. This process is primarily regulated by key molecular pathways involving p53, p21, p16, and the retinoblastoma protein (RB). DNA damage activates p53, which induces the expression of p21, a cyclin-dependent kinase (CDK) inhibitor [107,108]. p21 binds to CDK2 and cyclin E, thereby inhibiting RB phosphorylation and leading to G1 cell cycle arrest [107,109,110]. The p16 protein, in a different pathway, blocks CDK4 and CDK6, which also prevents RB phosphorylation and puts the cells into a state of permanent growth arrest [107,110]. In the case of ovarian cancer, overexpression of p16 has been shown to correlate with an increase in senescent cells and serves as a prognostic factor for a better response to therapy [111].

The senescence-associated secretory phenotype is a characteristic set of cytokines, chemokines, growth factors, and proteases secreted by senescent cells that can modify the tumor microenvironment [107]. SASP can have pro-inflammatory effects, attracting immune cells to the tumor microenvironment, which may support the elimination of cancer cells but also promote tumor growth and invasion depending on the context [112]. In ovarian cancer, SASP

induces the recruitment of macrophages and lymphocytes, which can lead to the elimination of cancer cells, but also to a chronic inflammatory state that supports tumor progression and resistance to chemotherapy [107].

The ability of cancer cells to evade apoptosis through senescence-related mechanisms may allow them to survive despite the use of cytotoxic drugs [108,113]. Studies have shown that low doses of chemotherapeutic agents, such as cisplatin, can induce cellular senescence instead of apoptosis, leading to a permanent growth arrest and reduced aggressiveness of cancer cells [107,114]. The expression of p16 and p21 is essential for the induction of senescence in response to cisplatin treatment, which suggests that increasing the activity of these pathways may be a strategy to overcome resistance [107,108,115,116].

3.3 Molecular Biomarkers of Senescence and Their Role in Therapy Prognosis

Numerous markers of cellular aging, such as p16, p21, and SA- β -gal, have been identified in cancer cells, although it is difficult to pinpoint a single biomarker that distinguishes senescence across all cell types [107,117]. p16, in particular, is a prognostic biomarker, whose overexpression correlates with a higher number of senescent cells and a better response to treatment [111]. Increased SA- β -gal expression indicates higher activity of the senescence process, and changes in the expression of these proteins after chemotherapy may serve as a marker of treatment response and predict the development of resistance [118,119]. In response to the challenges associated with drug resistance, biologic therapies targeting senescence pathways are gaining importance. Research has shown that activation of Wnt5a signaling induces senescence in ovarian cancer cells, and its modulation may increase the tumor's sensitivity to therapy [120]. Similarly, knockdown of RRM2 in ovarian cancer cell lines induces senescence, which inhibits tumor growth [121]. RNA interference with EZH2 induces senescence and cell cycle arrest, reducing the resistance of SKOV3/DDP cells to cisplatin [122].

Induction of cellular senescence may be an effective strategy to counteract drug resistance in ovarian cancer. Utilizing the p16-RB and p53-p21 pathways to induce cellular senescence, along with SASP induction, has therapeutic potential to modulate the tumor microenvironment and support immune elimination of cancer cells. Therapies that induce senescence through permanent cell cycle arrest represent an innovative therapeutic approach that can enhance the effectiveness of ovarian cancer treatment and limit its progression in the context of resistance to conventional therapies [107,108,117].

4. Cellular Senescence as a Mechanism Regulating Resistance to Chemotherapy

Cellular senescence is defined as the permanent arrest of the cell cycle, which cells enter in response to

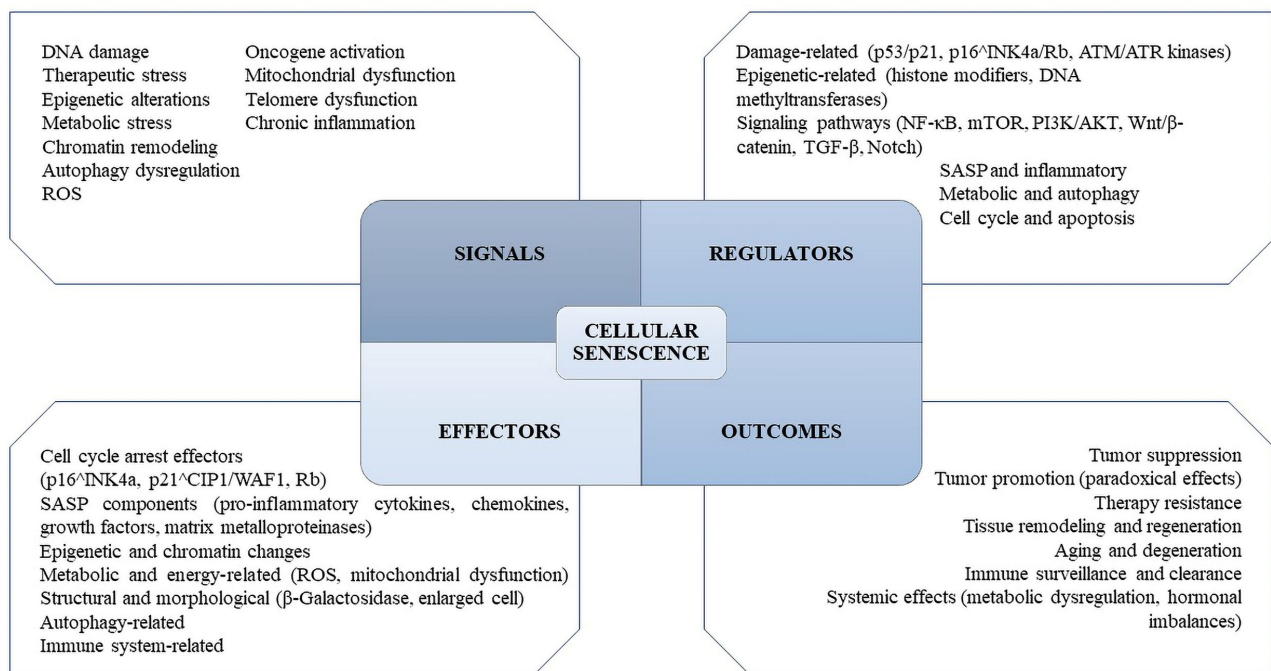


Fig. 1. Integrated framework of signals, regulators, effectors, and outcomes of cellular senescence.

stressors such as DNA damage, oxidative stress, and pro-inflammatory signaling. Although senescent cells stop dividing, they remain metabolically active, leading to phenotypic changes and gene expression that significantly impact the tumor microenvironment and treatment response [123,124]. In ovarian cancer, induction of senescence is a common result of therapy based on cisplatin and PARP inhibitors, which contributes to low treatment effectiveness, especially in advanced stages of the disease [125,126]. As a result of the action of chemotherapeutic agents such as cisplatin, DNA damage accumulates, activating the ATM/ATR and p53/p21 pathways, leading to cell cycle arrest and inducing cellular senescence [125,126,127,128]. Especially in cancer cells with mutations in DNA repair genes such as *BRCA1/2*, there is a higher tendency to induce aging, which in turn may increase resistance to PARP inhibitors [123,129].

Oxidative damage to DNA and proteins, resulting from excessive production of reactive oxygen species (ROS), is another key factor in inducing cells into a state of aging. Chemotherapy and radiotherapy further increase ROS levels, which activate senescence mechanisms as a cellular defense response [130,131]. The activity of antioxidant enzymes such as SOD (superoxide dismutase) tends to decrease in senescent cells, which increases their sensitivity to oxidative stress [130,131,132,133]. Conversely, activation of the NF- κ B and STAT3 pathways in senescent cells induces the secretion of pro-inflammatory mediators that modulate the tumor microenvironment [123,134,135]. Such an environment promotes the survival of cancer cells and their adaptation to anti-cancer treatment. It has been

shown that activation of NF- κ B increases resistance to PARP inhibitors, reducing the effectiveness of therapy [123,134].

The SASP Phenotype and Its Impact on Drug Resistance Through Modification of the Tumor Microenvironment

The SASP phenotype includes the secretion of various mediators such as IL-6, IL-8, MMP-3, and VEGF, which alter the tumor microenvironment (Fig. 2), promoting angiogenesis, growth, and migration of cancer cells. SASP can activate neighboring cancer cells, enhancing their survival and resistance to treatment [132,134,135]. SASP also affects immune system cells, altering immune responses and supporting immune tolerance to cancer cells [123,129].

Recent evidence indicates that specific miRNAs directly modulate the composition and paracrine activity of the SASP, thereby influencing immune cell infiltration, stromal cell activation, and angiogenesis [136,137]. For instance, miR-146a and miR-155 act as key regulators of SASP transcriptional output: miR-146a attenuates NF- κ B-driven secretion of IL-6 and IL-8, reducing chronic inflammation and promoting the clearance of senescent cells by immune effectors, whereas miR-155 amplifies pro-inflammatory SASP factors, enhancing recruitment of myeloid-derived suppressor cells (MDSCs) and promoting PD-L1 expression on tumor-associated macrophages, which supports immune evasion [138,139,140]. Other miRNAs, such as members of the miR-34 and miR-200 families, influence stromal remodeling by regulating SASP-associated matrix metalloproteinases (MMPs) and VEGF, thereby modulating angiogenesis and extracellu-

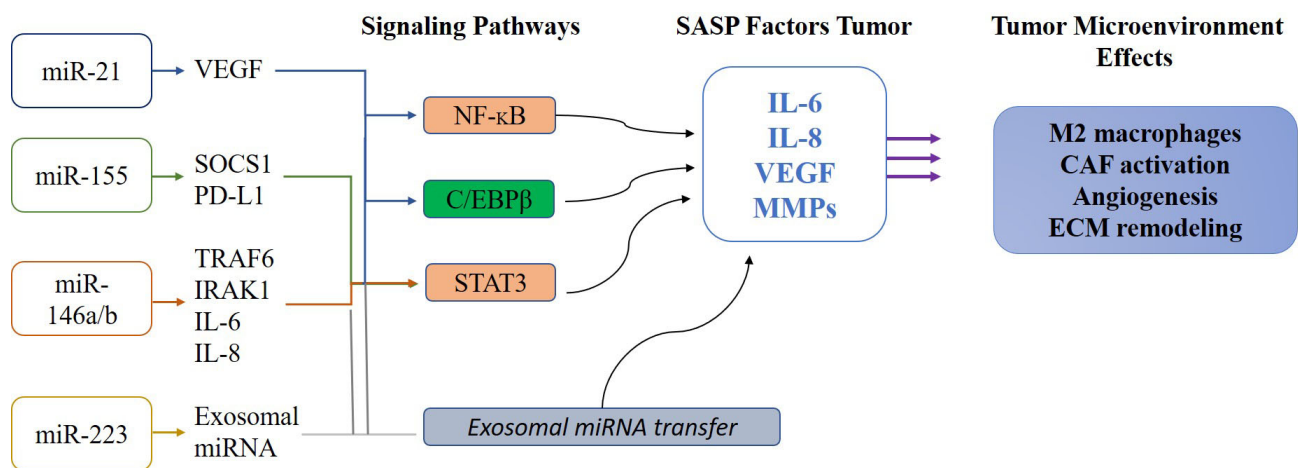


Fig. 2. miRNA–SASP–tumor microenvironment regulatory network. Selected miRNAs (miR-21, miR-155, miR-146a/b, miR-223) modulate SASP composition through NF-κB, C/EBPβ, and STAT3 signaling, directly regulating IL-6, IL-8, VEGF, and MMP expression. SASP factors promote immune cell polarization, cancer-associated fibroblast (CAF) activation, angiogenesis, and extracellular matrix remodeling, while exosomal miRNA transfer reinforces pro-tumorigenic signaling within the TME.

lar matrix dynamics [100,102,141,142,143,144]. These miRNA-SASP interactions establish a regulatory network in which miRNAs fine-tune senescence-driven crosstalk between cancer cells, immune infiltrates, and stromal elements, ultimately affecting tumor progression, therapy resistance, and the immunological landscape of the tumor microenvironment (Fig. 3).

It has been shown that exposure of cells to cisplatin increases the secretion of SASP factors, such as IL-6, which correlates with increased drug resistance. It has also been demonstrated that senescent cells can initiate an ‘escape from senescence’ phenotype, which enhances their ability to re-enter the cell cycle and supports the development of chemotherapy resistance [129,145,146]. It has also been confirmed that blocking the NF-κB pathway reduces SASP levels, thereby improving cancer cell sensitivity to PARP inhibitors, suggesting the potential of combining SASP-modulating agents with anticancer drugs [134,147,148]. The development of resistance to chemotherapy in ovarian cancer, associated with the induction of cellular aging, poses a significant clinical challenge, and further research on modifying the SASP phenotype may contribute to new therapeutic strategies (Fig. 3).

The intricate relationship among ovarian cancer stem cells (OCSCs), microRNA regulation, and cellular senescence constitutes a critical yet often underappreciated axis of therapy resistance in ovarian cancer. While classical mechanisms such as enhanced DNA repair (BRCA1/2 mutations, DNA polymerase eta activity) and inhibited apoptosis are well-established drivers of resistance, OCSCs exhibit distinct adaptive strategies, including metabolic plasticity and epigenetic reprogramming, which are often mediated by miRNAs and influenced by senescence. OCSCs, characterized by markers such as CD133, ALDH1, SOX2,

NANOG, and OCT4, exhibit significant metabolic plasticity that underpins their survival and therapeutic resistance [149,150,151]. Unlike differentiated tumor cells that predominantly utilize aerobic glycolysis (the Warburg effect), OCSCs often rely on oxidative phosphorylation (OXPHOS) and exhibit elevated mitochondrial respiration [149,152]. This metabolic shift provides energy for processes such as drug efflux and maintenance of stemness, notably supported by the upregulation of ALDH1 [149,151,152], which detoxifies reactive oxygen species (ROS) and contributes to chemoresistance [152].

The PI3K/AKT/mTOR pathway, frequently hyperactivated in OCSCs, further drives self-renewal, proliferation, and resistance, including an observed metabolic switch [149,152]. Metformin, an anti-diabetic drug, has shown promise in clinical trials by targeting OCSC metabolism, forcing a shift from OXPHOS to anaerobic glycolysis and suppressing proliferation and metastatic capacity [152,153]. This highlights a key difference from bulk tumor cells, where metabolic reprogramming in CSCs directly contributes to drug evasion. OCSCs display intrinsic resistance to platinum-based chemotherapy and PARP inhibitors, partly owing to their ability to maintain a low-proliferative, senescence-evading state rather than undergoing irreversible growth arrest.

Several miRNAs implicated in canonical senescence pathways also function as key modulators of stemness programs in OCSCs. For instance, the miR-200 family (miR-141, miR-200a, miR-200b, miR-200c, miR-429) functions as a tumor suppressor in many cancers, often by repressing TGF-β, thereby inhibiting EMT and drug resistance [154]. However, an “opposite voice” exists, where miR-200a can confer chemoresistance in breast cancer by antagonizing *TP53INP1* and *YAP1* [154,155]. Similarly, miR-34a, which

miRNA-driven regulatory nodes governing therapy-induced senescence and resistance

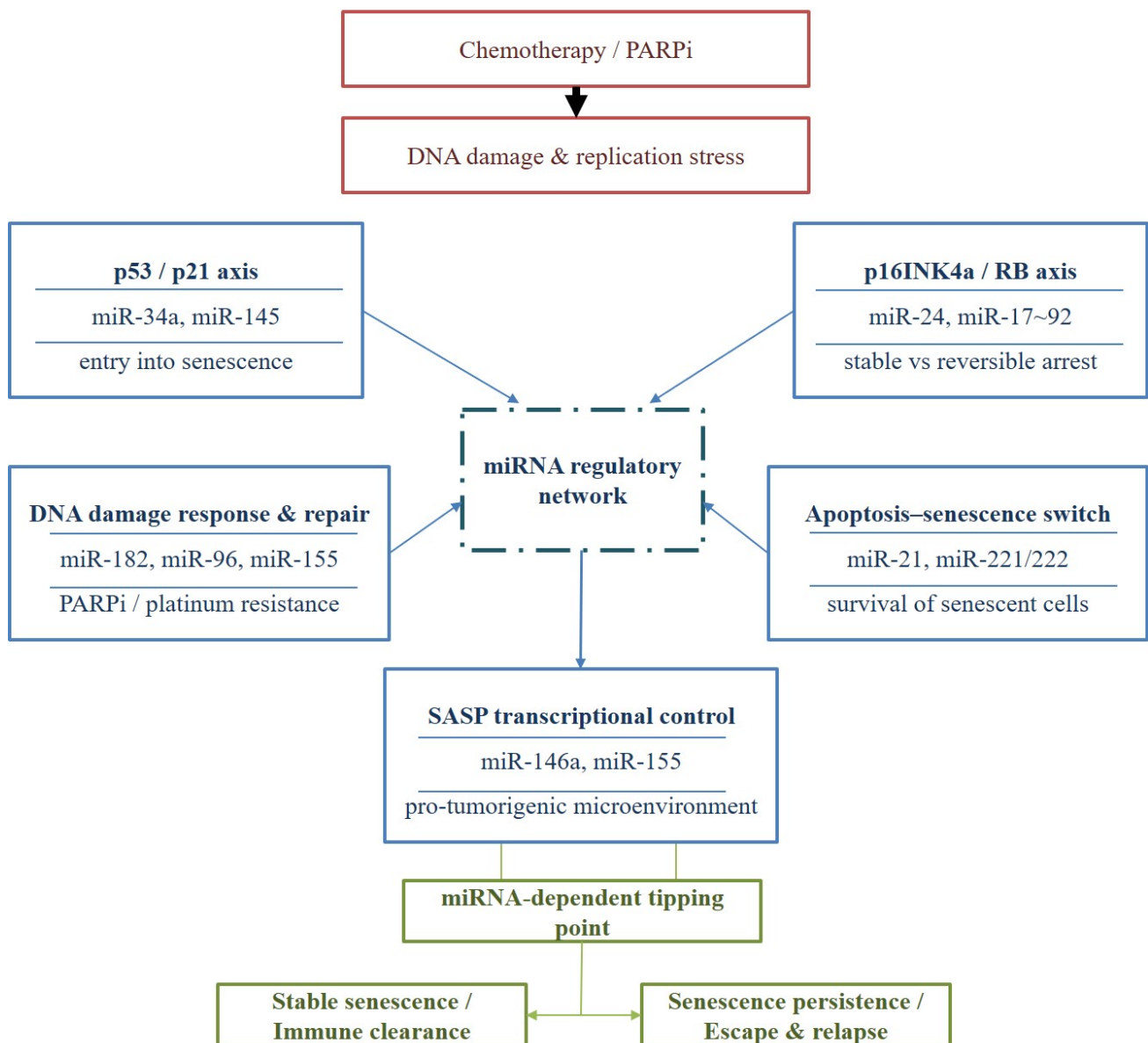


Fig. 3. miRNA-driven regulation of therapy-induced senescence and chemoresistance in ovarian cancer. Overview of miRNA-regulated pathways activated by chemotherapy or PARP inhibitors in ovarian cancer. Therapy-induced DNA damage engages multiple miRNA-controlled nodes, including the p53/p21 and p16INK4a/RB axes, DNA damage response and repair, apoptosis-senescence switching, and SASP transcriptional regulation. Integration of these pathways within an miRNA regulatory network determines a critical tipping point between stable senescence with immune clearance and senescence persistence associated with chemoresistance and tumor relapse.

typically enhances docetaxel sensitivity by targeting ZEB1, can have its anti-tumor effect attenuated by hypoxia [154]. The miR-34 family, as a well-established downstream effector of p53-mediated senescence, suppresses stemness-associated transcription factors and Notch signalling. Its downregulation in OCSCs has been linked to enhanced self-renewal capacity and chemoresistance [156,157,158]. Similarly, miR-145, which promotes senescence entry via repression of pluripotency factors (such as *OCT4*, *SOX2*, and

KLF4), is frequently silenced in stem-like ovarian cancer subpopulations, thereby favoring reversible arrest or quiescence rather than stable senescence [159,160].

Dysregulation of miRNAs like miR-21 [154,159] and miR-194-5p [159] has been linked to ovarian cancer tumorigenesis and chemoresistance, often through pathways involving IGF1R or STAT3. These miRNAs orchestrate a complex regulatory landscape that governs the balance between stemness and differentiation, thereby di-

rectly affecting therapeutic response. Oncogenic miRNAs such as miR-21 and miR-214 support CSC maintenance by attenuating apoptosis and reinforcing PI3K/AKT and Wnt/ β -catenin signaling, pathways known to antagonize p16INK4a/RB-dependent senescence [161,162]. Notably, emerging evidence suggests that therapy-induced senescence in bulk tumor cells may indirectly promote CSC survival via miRNA-regulated SASP, thereby creating a pro-stemness niche enriched in inflammatory cytokines and growth factors. miR-146a and miR-155, central regulators of SASP transcriptional output, have been implicated in shaping inflammatory microenvironments that sustain CSC plasticity and facilitate post-therapy tumor repopulation [138,163,164,165,166].

The crosstalk between stemness pathways and senescence regulators is particularly relevant for OCSC-mediated resistance. Cellular senescence, traditionally viewed as a tumor-suppressive mechanism involving cell cycle arrest (p53/p21, p16INK4a/RB pathways), has been increasingly recognized for its paradoxical role in promoting cancer progression and stemness [167]. Therapy-induced senescence (TIS) can lead to senescence bypass or escape in cancer cells, thereby restoring stemness [167,168]. In ovarian cancer, this can manifest as increased expression of stem-related markers (e.g., CD44, CD133, OCT4) and enhanced tumorigenicity after radiation therapy [134,167]. The senescence-associated secretory phenotype, a hallmark of senescent cells, plays a key role in reshaping the tumor microenvironment to support CSCs [167,168]. SASP components, including proinflammatory factors like IL-6 and IL-8, can create a chronic inflammatory milieu that promotes OCSC stemness and drug resistance [146,149,167]. For instance, IL-6 signaling, activated by platinum-based chemotherapy or secreted by cancer-associated fibroblasts (CAFs), promotes OCSC enrichment through STAT3 activation and increased ALDH1A1 expression [149]. This suggests that senescent cells, far from being inert, actively contribute to a supportive niche for OCSCs, enabling their survival and proliferation post-treatment.

The concept of senescence bypass or escape in OCSCs following chemotherapy or PARP inhibition is a critical area of ongoing research. While conventional therapies aim to eliminate tumor cells, they can inadvertently induce senescence in a subpopulation of cancer cells, which then reprogram to regain stemness. This acquired stemness can lead to resistance to platinum-based drugs and PARP inhibitors, contributing to the high recurrence rate of ovarian cancer [149]. The precise mechanisms underlying this reprogramming, including epigenetic modifications (e.g., changes in H3K9me3 and H3K27me3 patterns) [167,169] and metabolic shifts (e.g., altered OXPHOS function and ROS levels) [167,170], are still being elucidated. The ability of OCSCs to shift between quiescent and proliferative states, influenced by microenvironmental changes, further

highlights their adaptive capacity and the challenge they pose to eradication.

OCSC-mediated therapy resistance is not merely an outcome of classical DNA repair or apoptosis evasion, but a complex interplay involving unique metabolic adaptations, intricate miRNA regulatory networks, and the paradoxical effects of cellular senescence. The ability of OCSCs to escape senescence or leverage SASP components to create a pro-stemness niche represents a significant hurdle in achieving durable responses in ovarian cancer. A deeper understanding of these interconnected mechanisms is crucial for developing novel combination therapies that target both bulk tumor cells and the resilient OCSC population, ultimately improving patient outcomes. Key open questions remain regarding the precise triggers for senescence escape in OCSCs, the specific miRNA-SASP interactions that drive stemness, and the development of clinically validated biomarkers to track these processes. Translational efforts should prioritize strategies that disrupt these OCSC-miRNA-senescence axes to overcome resistance and prevent recurrence.

5. The Role of miRNA in Modulating Cellular Senescence and Drug Resistance

Accumulating evidence indicates that chemoresistance in ovarian cancer is not driven by isolated molecular events but rather arises from the coordinated interaction between dysregulated signaling pathways, epigenetic reprogramming, and adaptive cellular responses to therapeutic stress. Within this regulatory landscape, cellular senescence is an important adaptive process that links DNA damage responses, oxidative stress, and cell cycle control to durable phenotypic alterations, including stable growth arrest and the development of a senescence-associated secretory phenotype (Table 2). These senescence-associated changes profoundly influence tumor cell plasticity, intercellular communication, and remodeling of the tumor microenvironment, thereby shaping therapeutic outcomes. MicroRNAs emerge as key upstream regulators of this continuum by fine-tuning multiple components of senescence-related signaling networks and coordinating downstream effects on apoptosis, epithelial-mesenchymal transition, immune modulation, and drug sensitivity (Fig. 4). Understanding the regulatory cascade that connects miRNA-mediated pathway control to senescence-associated phenotypes and, ultimately, to therapeutic response is therefore critical for the rational design of strategies aimed at overcoming chemoresistance. The following section focuses on the mechanistic role of miRNAs in modulating cellular senescence and drug resistance in ovarian cancer.

Many miRNAs play a key role in regulating senescence by affecting the expression of genes involved in cell cycle arrest and DNA repair mechanisms (Figs. 4,5). For example, miR-34a, one of the most well-known aging-related miRNAs, is activated by p53 and regulates the ex-

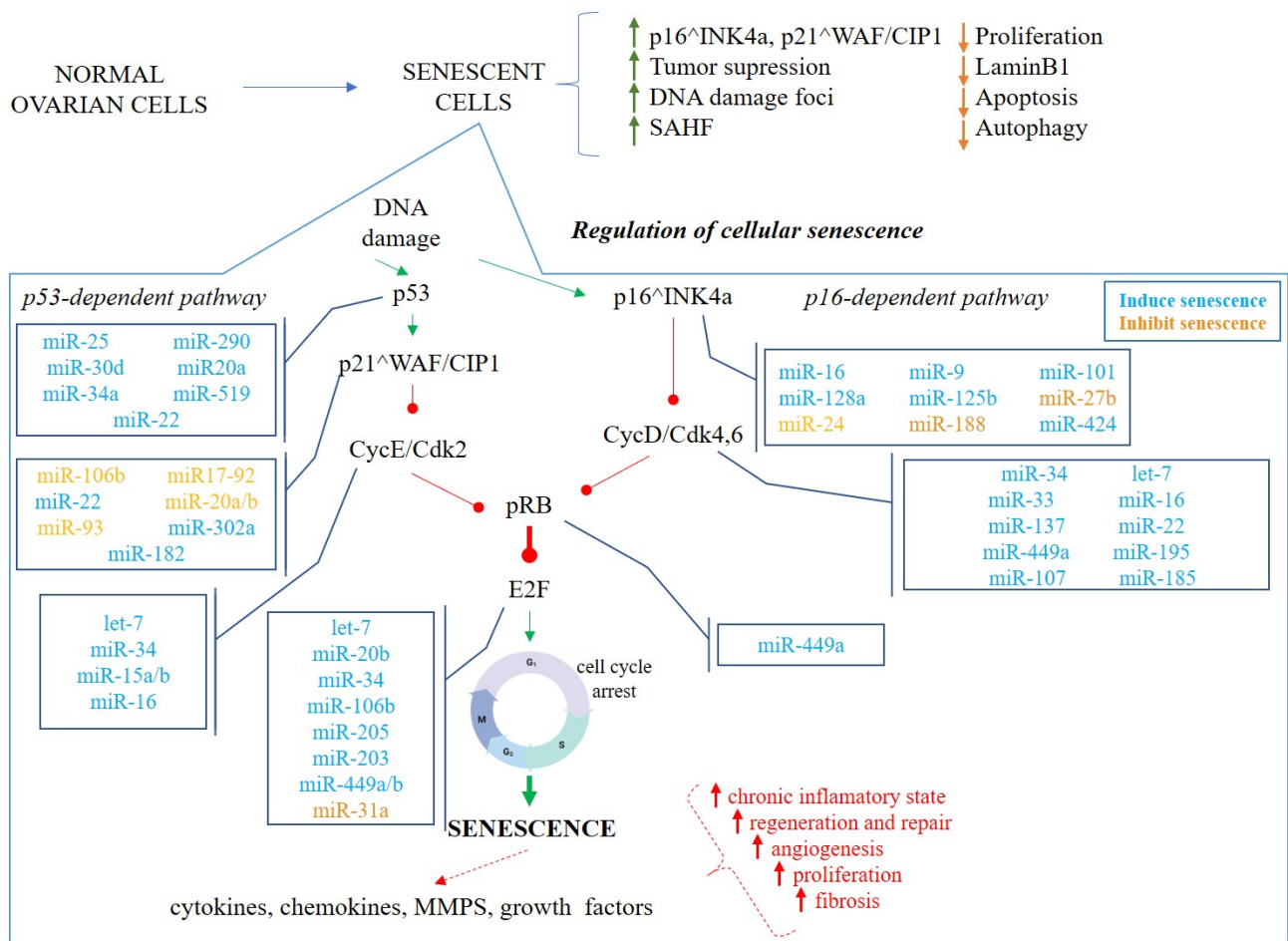


Fig. 4. MicroRNA-mediated regulation of cellular senescence pathways in ovarian cells. ↑, upregulation; ↓, downregulation.

pression of genes responsible for cell cycle arrest, such as cyclin *E2* and *CDK4* [141,142,171]. MiR-34a additionally decreases the level of *SIRT1*, which leads to increased p53 activity and promotes cellular aging, increasing the cells' sensitivity to stress induced by treatment, including cisplatin-based chemotherapy [156,171]. On the other hand, miR-21, considered an oncogenic miRNA, plays a significant role in promoting drug resistance by inhibiting apoptosis and supporting the survival of cancer cells. The mechanism of miR-21 involves reducing the expression of pro-apoptotic genes such as *PTEN* and *BAX*, which leads to activation of the PI3K/AKT/mTOR pathway, enhancing survival signaling and supporting adaptation to stressful conditions [85,172,173,174]. Studies have shown that overexpression of miR-21 correlates with resistance to cisplatin and increased invasiveness of cancer cells [175,176]. Furthermore, miR-146a plays a complex role in the context of cellular aging, modulating both pro-inflammatory and anti-inflammatory processes in the tumor microenvironment [165,177]. MiR-146a influences the activity of the NF- κ B pathway, regulating the expression of pro-inflammatory mediators such as IL-6 and IL-8, which are key to the SASP phenotype [138,178,179]. Inhibition

of miR-146a/b can increase secretion of these mediators, thereby promoting the development of a treatment-resistant phenotype, whereas its overexpression may reduce the inflammatory response and support the elimination of senescent cells [138,179].

The overexpression of miR-433 induces cellular senescence by increasing paclitaxel resistance in ovarian cancer cells. This mechanism involves the modulation of cyclin-dependent kinase (CDK) expression and related transcription factors. miR-433-associated senescence leads to the accumulation of secretory factors related to the secretory phenotype, which promotes a pro-tumorigenic microenvironment and therapy resistance [180]. Meanwhile, miR-506 exhibits anti-cancer activity by inhibiting proliferation and inducing senescence through regulation of the CDK4/6-FOXO1 axis [181]. This action arrests the cell cycle in the G1 phase and reduces the activity of factors promoting tumor growth. MiR-509-3p increases the sensitivity of ovarian cancer cells to cisplatin by inhibiting anti-apoptotic genes such as *BCL2*, *BCL2L2*, and *MCL1*. The induction of apoptosis in response to cisplatin is largely associated with cellular senescence, in which cells retain the ability to secrete pro-inflammatory mediators and factors

INTEGRATED MODEL OF CHEMORESISTANCE IN OVARIAN CANCER

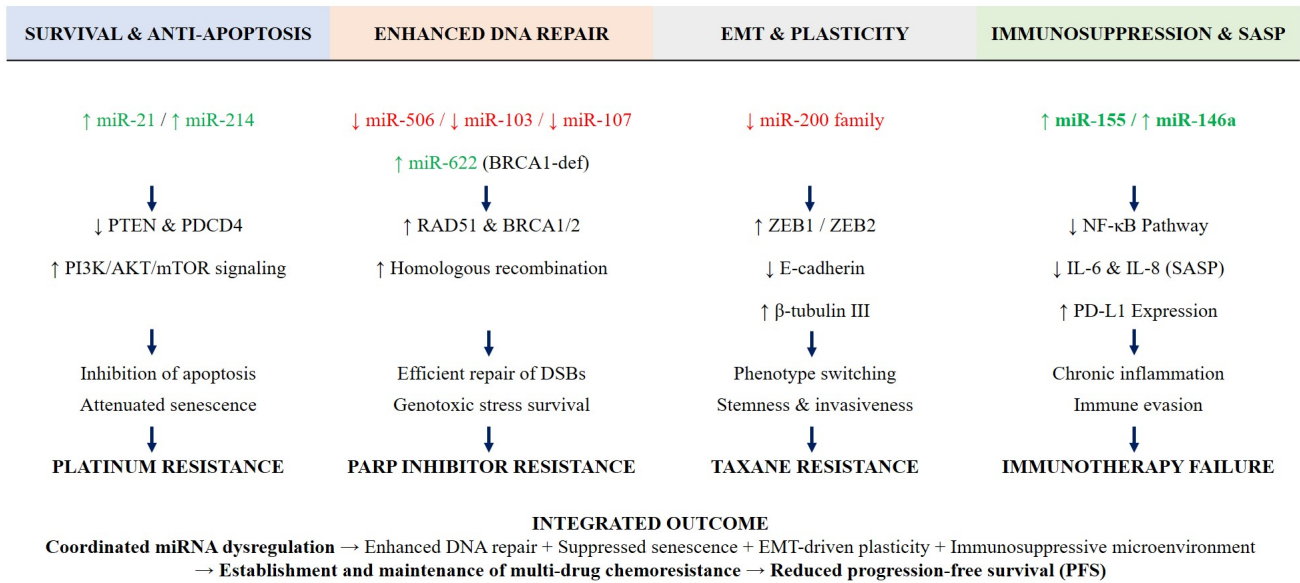


Fig. 5. Integrated miRNA-driven model of chemoresistance in ovarian cancer. From a clinical perspective, altered miRNA expression supports tumor adaptation to therapeutic pressure, allowing cancer cells to persist despite treatment and facilitating disease recurrence. By linking intrinsic resistance mechanisms with immune evasion and microenvironmental remodeling, miRNAs contribute to reduced treatment responsiveness, shorter progression-free survival, and limited long-term benefit from current therapeutic strategies.

that promote the survival of neighboring cancer cells. It has been shown that miR-509-3p reduces the expression of *BCL2*, *BCL2L2*, and *MCL1*, leading to increased activation of apoptosis in SKOV3 and OVCAR3 cell lines treated with cisplatin. This regulation occurs at the translational level through miRNA binding to the 3' UTR regions of these genes [182]. Similarly, other miRNAs, such as miR-199a/214, modulate pathways associated with drug resistance and stemness maintenance in cancer cells. Epigenetic and genetic changes in miRNA clusters, such as miR-199a/214 or miR-200c/141, are crucial for regulating processes associated with drug resistance and senescence in ovarian cancer. For example, miR-200c/141 regulates EMT and sensitivity to cisplatin by modulating the KEAP1-Nrf2 pathway. Conversely, miR-199a and miR-214 regulate gene expression in AKT signaling and the β-catenin pathway, thereby affecting the survival and chemoresistance of cancer cells [183]. miRNAs from the miR-183/182/96 cluster also contribute to the regulation of apoptosis mechanisms and chemoresistance in ovarian cancer by modulating the expression of genes such as *PDCD4* and *SMAD4*. For example, miR-182 increases resistance to cisplatin while promoting the proliferation of cancer cells [184].

Cancer cells in a senescent state produce SASP, which supports tumor spread and modulation of the immune response. miRNAs, such as the miR-106b~25 cluster, can regulate SASP by modulating the expression of adhesion proteins like E-cadherin and transcription factors such as

EP300, thereby increasing the motility and invasiveness of cancer cells [185,186]. The p21 pathway, an important factor in halting the cell cycle, is regulated by miRNAs such as miR-17-5p, which inhibit its expression, allowing proliferation to continue even in the presence of DNA damage. The interaction of miRNAs with the p21 pathway may therefore play a key role in modulating cellular aging, affecting the response to chemotherapeutic drugs [107,187]. The RB pathway, associated with cell cycle regulation and growth arrest, is also modulated by miRNAs such as miR-29, which can influence its phosphorylation, promoting the transition from the G1 to S phase, thereby facilitating cell cycle progression and reducing the effectiveness of cancer therapies [58,188,189].

In Table 3 (Ref. [32,34,35,82,85,91,96,98,103,138,141,142,143,156,165,166,171,172,175,176,177,178,180,181,182,183,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228]), SA-miRNAs were categorized based on their predominant functional impact on cellular senescence and therapy response. Pro-senescence miRNAs are defined as miRNAs that induce canonical senescence hallmarks, including activation of the p53/p21/p16 axis, senescence-associated β-galactosidase (SA-β-gal) activity, senescence-associated heterochromatin foci (SAHF), and/or the senescence-associated secretory phenotype. These miRNAs typically enhance therapeutic sensitivity, although in some contexts they may exert dual effects by

Table 3. Representative microRNAs involved in cellular senescence and their impact on chemotherapy resistance in ovarian cancer.

miRNA	Classification	Main targets/pathways	Effect on senescence	Evidence (model)	Impact on therapeutic resistance	Ref.
miR-34a	Pro-senescence	p53 axis, <i>SIRT1</i> , <i>CDK4</i>	Promotes senescence via p53 activation and <i>E2</i> , <i>SIRT1</i> inhibition	<i>in vitro/in vivo</i> , mechanistic studies	Increases sensitivity to cisplatin and other cytotoxics.	[141,142,156,171]
miR-21	Anti-senescence/oncomiR	<i>PTEN</i> , <i>BCL2</i> → PI3K/AKT/mTOR	Suppresses senescence, promotes survival	cell lines, preclinical	Associated with resistance to cisplatin, taxanes and PARP inhibitors.	[82,85,172,175,176,190]
miR-146a	Context-dependent/SASP regulator	<i>NF-κB</i> , regulation of <i>IL-6/IL-8</i> , SASP	Can attenuate or modulate SASP, context-dependent pro/anti-senescence effects	cell and inflammatory/senescence models	Modulates resistance indirectly via TME and inflammatory signalling.	[34,138,165,177,178]
miR-155	Pro-senescence (SASP-promoting)	<i>FOXO3a</i> , <i>BCL6</i> , <i>NF-κB</i>	Supports SASP and pro-inflammatory senescence programs	inflammatory and oncologic models	Linked to therapy resistance through immune modulation (e.g., PD-L1) and chronic inflammation.	[166,191,192,193]
miR-29 (family)	Pro-senescence	RB/E2F axis, <i>HDAC4</i> , epigenetic regulators	Promotes senescence (epigenetic reprogramming)	mechanistic cell studies, reviews	May increase sensitivity to alkylating agents and HDAC inhibitors.	[194,195,196]
miR-125b	Anti-senescence	<i>p53</i> , <i>BAX</i> (negative regulators)	Inhibits senescence by down-regulating p53/BAX pathways	<i>in vitro</i> /functional studies	Associated with increased resistance to cisplatin and other therapies.	[197,198,199,200]
miR-10b	Anti-senescence (indirect)	<i>HOXD10</i> , RhoC → EMT	Promotes EMT and invasiveness, may facilitate bypass of senescence	<i>in vitro/in vivo</i> metastasis models	Promotes resistance through EMT-linked mechanisms.	[201,202,203,204]
miR-93	Anti-senescence	<i>p21</i> , <i>TGF-β</i> , <i>PTEN</i>	Suppresses p21 & related checkpoints → avoids cell-cycle arrest	cellular functional studies	Supports chemoresistance by preventing arrest/apoptosis.	[205,206,207]
miR-200c (miR-200 family)	Pro-senescence/anti-EMT	<i>ZEB1/ZEB2</i> → E-cadherin, <i>KEAP1-Nrf2</i>	Can stabilize epithelial phenotype, facilitating senescence programs	clinical and preclinical data	Reduces EMT-mediated resistance, correlates with improved sensitivity in some settings.	[98,103,143,208,209,210]
miR-182	Anti-senescence	<i>BRCA1</i> , <i>FOXO1</i> , HR regulation	May impair senescence via DDR modulation	cell lines, mechanistic reports	Complex effects—can modulate DNA-repair and influence sensitivity to DNA-damaging agents.	[91,211,212,213]
miR-210	Anti-senescence (hypoxia adaptation)	<i>HIF-1α</i> , <i>E2F3</i>	Promotes adaptation to hypoxia, may inhibit senescence under low-O ₂ stress	hypoxia and tumor models	Supports survival under hypoxia → contributes to therapy resistance.	[214,215,216,217]
miR-203	Pro-senescence/tumor suppressor	<i>ATM</i> , <i>DNMT3b</i> , <i>ANP63</i>	Modulates DDR and epigenetics, may promote senescence	<i>in vitro</i> /preclinical	Can improve response to DNA-damaging therapies.	[218,219,220]
miR-370	Pro-senescence	<i>IGF1R</i> , <i>DICER</i>	Inhibits proliferative signalling → senescence features	cell-based evidence	Reduces chemoresistance in some ovarian models.	[183,221,222]
miR-424	Pro-senescence/immunomodulatory	<i>c-MYC</i> , <i>BCL2</i> , <i>CDK6</i>	Induces cell-cycle arrest and pro-apoptotic signalling	mechanistic studies	May sensitize cells by promoting apoptosis and reducing resistance.	[35,183,223,224]
miR-223	Contextual (EMT/exosomal transfer)	<i>FBXW7</i> , β-catenin	Can support EMT-associated phenotypes, variable effects on senescence	exosome and <i>in vivo</i> evidence	Facilitates transfer of resistance via extracellular vesicles/EMT.	[225,226,227,228]

Table 3. Continued.

miRNA	Classification	Main targets/pathways	tar-	Effect on senescence	Evidence (model)	Impact on therapeutic resistance	Ref.
miR-433	Pro-senescence (TIS-related)	CDK regulators (indirect)		Induces therapy-induced senescence and SASP accumulation	cell models, functional studies	Paradoxically associated with increased paclitaxel resistance via SASP effects.	[180]
miR-506	Pro-senescence/tumor suppressor	<i>CDK4/6</i> <i>FOXMI</i>	→	Induces G1 arrest and senescence	<i>in vitro</i> /preclinical ovarian studies	Enhances chemosensitivity and reduces resistance.	[32,96,181]
miR-509-3p	Pro-senescence/apoptotic enhancer	<i>BCL2</i> , <i>BCL2L2</i> , <i>MCL1</i>		Promotes apoptosis and is linked to senescent/apoptotic responses	SKOV3/OVCAR3 models	Increases cisplatin-induced apoptosis and sensitivity.	[182]

concomitantly activating SASP (e.g., miR-34a, miR-29, miR-506, miR-424). In contrast, anti-senescence miRNAs suppress cell-cycle arrest and DNA damage response pathways, thereby promoting survival and senescence escape, and are frequently classified as oncomiRs (e.g., miR-21, miR-125b, miR-93). A third group comprises miRNAs targeting specific resistance pathways, whose primary function is linked to distinct mechanisms of therapeutic resistance rather than global regulation of senescence, such as homologous recombination restoration (HR/BRCA), RAD51-mediated DNA repair, ABC transporter activity, EMT, or SASP-driven immune evasion. These miRNAs are indicated as pathway-oriented subgroups within the table (e.g., miR-622 associated with HR rescue; miR-493-5p involved in replication fork stabilization).

The SASP phenotype, characterized by the secretion of pro-inflammatory cytokines, chemokines, proteases, and growth factors, is an integral part of cellular senescence that influences the tumor microenvironment and supports the development of drug resistance [123,134,146]. Many miRNAs play a key role in modulating SASP. For example, miR-21 stimulates NF- κ B activity, leading to increased secretion of IL-6 and IL-8, which promote angiogenesis, tumor cell growth, and the development of drug resistance [82,83,85,175]. On the other hand, miR-146a acts as a negative regulator of SASP, reducing the secretion of pro-inflammatory cytokines and supporting the elimination of senescent cells in the tumor microenvironment [34,138,165,178]. Accordingly, modulation of miRNA activity emerges as a promising therapeutic strategy in ovarian cancer, particularly through targeting regulatory mechanisms of the SASP, which may enhance chemosensitivity and suppress the emergence of drug-resistant phenotypes.

6. Therapeutic Strategies Based on miRNA Modulation to Overcome Drug Resistance

The application of miRNA as potential therapeutic agents in the treatment of drug-resistant ovarian cancer is based on the assumption that restoring the homeostasis of the miRNA network can induce a state of cellular senescence, leading to the cessation of proliferation and migration of cancer cells. Appropriately selected miRNAs, called senescence-associated miRNAs (SA-miRs), may serve as ‘mimics’ of tumor suppressors or inhibitors of oncogenic miRNAs (oncomirs) [42]. Mimic miRs are synthetic, double-stranded RNA molecules that imitate the activity of miRNAs with suppressive properties, such as miR-34a or miR-200c. Conversely, anti-miRNAs (anti-miRs) are chemically modified oligonucleotides, such as LNA (locked nucleic acids) or oligonucleotides with 2'-O sugar modifications, which neutralize the activity of oncogenic miRNAs [229,230]. An alternative method for eliminating oncogenic miRNAs is the use of so-called miRNA sponges, which bind these molecules and prevent their interactions with target genes. miRNA sponges can contain

sequences that bind to various miRNAs, which increases their therapeutic potential; however, this requires precise calibration of their expression levels [231,232,233].

The challenge in ovarian cancer therapy is the heterogeneity of the tumor, which makes it difficult to use a single miRNA to effectively inhibit tumor growth. Therefore, it is necessary to select a panel of miRNAs that collectively regulate key oncogenic pathways [79,190,234,235]. However, it is worth emphasizing that each of the selected miRNAs can regulate dozens of target genes, which increases the risk of adverse effects. Therefore, preclinical studies rely on advanced bioinformatics analyses that allow for precise modeling of the miRNA interaction networks and their targets [236,237,238,239,240].

6.1 Methods of Delivering SA-miRNA to Cancer Cells

One of the principal challenges in the therapeutic application of senescence-associated microRNAs is their efficient and safe delivery to target cancer cells. This limitation arises from several intrinsic biological barriers, including low cellular uptake efficiency, rapid degradation by circulating nucleases, renal clearance, and insufficient accumulation within tumor tissue [42,241]. Importantly, in the clinical setting, effective miRNA delivery is not only about improving molecular stability but also about achieving selective tumor targeting to maximize therapeutic efficacy while minimizing systemic toxicity and off-target effects.

To date, multiple delivery strategies have been developed for synthetic anti-miRNAs and miRNA mimics in ovarian cancer, including liposomes, lipid and polymeric nanoparticles, extracellular vesicles, viral vectors, aptamer-based systems, CRISPR-mediated genome modulation, and miRNA sponge technologies [242,243,244,245,246]. Among these approaches, lipid-based nanoparticles and polymeric nanocarriers remain the most extensively investigated and translationally advanced platforms, whereas extracellular vesicles and biologically inspired targeting systems represent emerging strategies with substantial clinical potential (Table 4, Ref. [241,242,243,245,247,248,249,250,251,252,253,254]).

6.1.1 Liposomal and Nanoparticle-Based Delivery Systems

Liposomes and lipid nanoparticles (LNPs) constitute well-established delivery vehicles for nucleic acid-based therapeutics. Their physicochemical properties enable efficient cellular internalization and protection of miRNA cargo from nuclease-mediated degradation. In ovarian cancer models, lipid-based nanoparticles have been shown to enhance miRNA bioavailability, induce cellular senescence, and suppress signaling pathways associated with chemoresistance [245,247,248]. Preclinical studies provide compelling evidence for their antitumor activity. In murine ovarian cancer models, cationic liposomes delivering miR-124 or miR-152 to SKOV3ip1 cells significantly reduced

Table 4. Comparative technical overview of miRNA delivery platforms evaluated in ovarian cancer (based on [241,242,243,245,247,248,249,250,251,252,253,254]).

Platform	Delivery characteristics and mechanisms	Representative miRNA and experimental context in ovarian cancer	Principal advantages	Key technical limitations
Lipid-based nanoparticles (LNP/liposomes)	Electrostatic encapsulation of miRNA, uptake predominantly via endocytosis and membrane fusion, ionizable lipids enable pH-dependent endosomal escape	miR-34a, miR-145, miR-200c, miR-199a-3p, <i>in vitro</i> OC cell lines and intraperitoneal/systemic murine models	High delivery efficiency, clinically validated manufacturing, suitability for intraperitoneal administration	Immunostimulatory responses, preferential hepatic accumulation, limited tumor specificity
Polymeric nanoparticles (PLGA-based)	Encapsulation within biodegradable polymer matrix, slow, controlled release, uptake via endocytosis	miR-34a, miR-145, anti-miR-21, xenograft OC models, often combined with chemotherapy	Favorable safety profile, prolonged local retention, tunable release kinetics	Suboptimal endosomal escape, formulation-dependent variability
Cationic polymer complexes (PEI-based)	Strong electrostatic condensation of miRNA, proton sponge-mediated endosomal escape	miR-34a, anti-miR-21, primarily <i>in vitro</i> and early <i>in vivo</i> OC models	High transfection efficiency, effective cytosolic release	Charge-related cytotoxicity, nonspecific biodistribution
Gold nanoparticles (AuNP)	Surface-conjugated miRNA, uptake via endocytosis, often combined with targeting ligands	miR-31, miR-375, miR-96/182, OC cell lines and xenograft models	Excellent physicochemical stability, facile functionalization	Lack of biodegradability, long-term tissue retention
Extracellular vesicles (exosomes)	Endogenous or engineered loading of miRNA, cellular entry via membrane fusion and receptor-mediated endocytosis	miR-145, miR-199a-3p, miR-34a, OC xenografts and tumor microenvironment studies	High biological compatibility, low immunogenicity, efficient cytosolic delivery	Limited scalability, heterogeneity, complex standardization
Cell-penetrating peptides (CPP)	Non-covalent peptide-miRNA complexes, direct translocation and endocytic uptake	miR-34a, let-7 family, anti-miR-21, <i>in vitro</i> and early <i>in vivo</i> OC studies	Sequence-defined targeting, minimal carrier mass, theranostic potential	Rapid clearance, susceptibility to proteolytic degradation
Viral vectors	Genomic encoding of pri-/pre-miRNA, receptor-mediated entry and nuclear expression	miR-34a, miR-143/145, mechanistic OC models	Sustained miRNA expression, high delivery efficiency	Immunogenicity, insertional mutagenesis risk, low clinical acceptability

tumor volume, demonstrating effective inhibition of tumor growth [255]. Similarly, neutral DOPC liposomes encapsulating miR-192 resulted in a marked reduction in tumor burden, confirming that non-cationic formulations may also achieve therapeutic efficacy [256]. Liposomal delivery of miR-106a restored chemosensitivity in cisplatin-resistant OVCAR3/CIS cells, highlighting the potential of miRNA-based strategies to overcome drug resistance [257]. Further refinements include receptor-targeted formulations, such as folate-conjugated liposomes carrying miR-18a, which reduced tumor mass in cisplatin-resistant ovarian cancer models [258], and integrin-targeted hybrid liposomes co-

delivering miR-497 and triptolide, which exhibited superior antitumor activity compared with non-anchored miRNA formulations [259].

Despite these encouraging preclinical data, clinical translation of liposomal miRNA delivery has proven challenging. The first systemically administered miRNA therapeutic to enter clinical evaluation, MRX34 (a liposomal miR-34a mimic), demonstrated pharmacodynamic activity and preliminary antitumor signals in a phase I trial involving patients with advanced solid tumors [260,261]. However, the study was prematurely terminated due to severe immune-related adverse events, including cytokine release

syndrome and hepatotoxicity, underscoring the prominent immunogenicity associated with systemic lipid-based miRNA delivery. These findings highlight a major translational bottleneck and emphasize the need for improved carrier design, dosing strategies, and immune monitoring in future clinical trials.

6.1.2 Polymeric Nanocarriers and Aptamer-Guided Targeting Approaches

Biocompatible polymers, such as chitosan or copolymers of poly(lactic-co-glycolic acid; PLGA), represent another important class of SA-miRNA delivery systems. Their electrostatic properties facilitate efficient binding of negatively charged miRNAs while protecting them from enzymatic degradation [246,249,262]. Importantly, polymeric carriers offer high modularity and can be functionalized with targeting ligands, including aptamers, to enhance tumor specificity. These systems can be modified through conjugation with aptamers targeted at specific receptors on cancer cells, such as EpCAM [219,263,264]. In ovarian cancer, EpCAM-specific aptamers have been employed for the targeted delivery of miR-203b-3p, a key regulator of cancer cell proliferation, migration, and drug resistance [219]. MiR-203b-3p suppresses the expression of resistance-associated genes such as ABCB1 and BCL2 and promotes senescence in ovarian cancer cells [218]. Aptamer/miR-203b-3p chimeras selectively targeted EpCAM-overexpressing cells, resulting in reduced tumor growth and invasiveness [219]. Encapsulation of such constructs within PLGA nanoparticles further enhanced miRNA stability and enabled controlled release, offering a promising approach for the treatment of chemoresistant tumors. Additional studies demonstrated that PEGylated PLGA nanoparticles decorated with the AS1411 aptamer and loaded with anti-miR-21 effectively reduced miR-21 levels in cisplatin-resistant A2780 cells, thereby reversing drug resistance and increasing cisplatin cytotoxicity [265]. Similar strategies targeting miR-214, which promotes chemoresistance via PTEN inhibition and activation of the PI3K/Akt pathway, resulted in enhanced chemosensitivity and improved therapeutic outcomes [266].

6.1.3 Extracellular Vesicles as Emerging miRNA Delivery Platforms

Extracellular vesicles, particularly exosomes, have attracted increasing attention as natural nanocarriers for miRNA delivery due to their high biocompatibility, intrinsic ability to cross biological barriers, and reduced immunogenicity [244,246,267,268,269]. In ovarian cancer models, exosomes derived from peritoneal fibroblasts of patients were shown to efficiently deliver miR-199a-3p following electroporation-based loading. Treatment of ovarian cancer cell lines resulted in downregulation of c-Met expression and inhibition of proliferation and invasion, while *in vivo* administration significantly reduced peritoneal dissemina-

tion and suppressed ERK and MMP2 activity [267,268]. From a translational perspective, exosome-based RNA delivery systems have recently entered early-phase clinical evaluation, reporting favorable safety profiles and evidence of target engagement. Nevertheless, their broader clinical application remains limited by substantial manufacturing and regulatory challenges, including low production yield, batch-to-batch variability, heterogeneity of vesicle populations, and the lack of standardized GMP-compliant production and quality control protocols.

6.1.4 Gene-Editing and miRNA Neutralization Strategies

CRISPR/Cas9 technology represents an alternative approach to miRNA modulation, enabling either permanent expression of therapeutic miRNAs or precise editing of endogenous miRNA loci [270]. In ovarian cancer models, CRISPR-mediated deletion of miR-137 increased cell proliferation, confirming its tumor-suppressive role (in A2780 cells), whereas targeting miR-21 reduced proliferation, migration, epithelial-mesenchymal transition, and enhanced chemosensitivity (in SKOV3 and OVCAR3 cell lines) [270,271]. Additionally, the loss of miR-21 inhibited EMT, leading to increased expression of epithelial markers (e.g., E-cadherin) and decreased expression of mesenchymal markers (e.g., vimentin) [272]. Additionally, the cells became more sensitive to chemotherapy, highlighting the potential of CRISPR in targeted ovarian cancer therapy. Although highly precise, CRISPR-based strategies face significant translational barriers related to delivery efficiency, immunogenicity of viral vectors, and regulatory considerations.

MiRNA sponge systems provide another strategy for neutralizing oncogenic miRNAs by competitively sequestering them and restoring tumor suppressor signaling. Synthetic and circRNA-based sponges targeting miR-21, miR-221, or miR-3652 have demonstrated the ability to inhibit EMT, suppress NF- κ B and STAT3 signaling, and restore cell-cycle regulators such as p21 and p27 [231,232,233,273]. In cancer therapy, including ovarian cancer, miRNA sponges can be used to restore balance in the regulation of molecular pathways related to tumor aggressiveness and drug response [231,233,274,275,276,277]. Synthetic and circRNA-based miRNA sponges are effective tools for modulating the expression of oncogenic miRNAs, such as miR-21 and miR-221, which play a significant role in ovarian cancer progression. These sponges work by competitively binding miRNAs via multiple complementary sequences, thereby blocking their function and restoring the expression of tumor suppressor proteins such as PTEN. In particular, circRNA-based sponges, characterized by high stability and a long half-life, can effectively silence miRNAs and thus inhibit activation of the PI3K/AKT and EMT pathways, which are crucial for the development and metastasis of ovarian cancer [278]. The combination of a sponge system with natu-

ral compounds such as curcumin can modulate the expression of miRNAs, including miR-200c and miR-365. Curcumin, acting as a miRNA suppressor, contributes to the inhibition of EMT (epithelial–mesenchymal transition) and the migration of cancer cells [279]. Sponge systems can regulate the expression of miR-3652, which affects NF- κ B and STAT3 signaling pathways, leading to the inhibition of pro-inflammatory processes and the proliferation of cancer cells. For example, functional miR-3652 sponges work by neutralizing its activity and stabilizing proteins responsible for cell cycle control, such as p21 and p27 [280]. However, these approaches remain largely preclinical, with delivery and durability representing key obstacles to clinical translation.

6.1.5 Viral Vectors

Viral vectors, such as adenoviral and lentiviral vectors, are among the most advanced methods for delivering miRNA to cancer cells. In the case of miRNA, these vectors can be modified to precisely target ovarian cells, ensuring high efficiency and long-lasting effects [246,250,281,282]. It has been shown that oncolytic viruses (OVs) can effectively deliver miRNA to myeloid cells within the tumor microenvironment by increasing the production of extracellular vesicles (TDEV) containing miRNA, which are preferentially taken up by tumor-associated macrophages (TAM). Infection with OV-miR-155 and OV-miR-19a reversed the immunosuppressive activity of TAM, improving T lymphocyte proliferation and the survival of mice with ovarian cancer, demonstrating the effectiveness of miRNA as immunomodulatory tools in oncolytic therapy [283].

7. Conclusion and Future Perspectives

Senescence-associated microRNAs are emerging as key regulators linking therapy-induced senescence to treatment resistance. Preclinical evidence indicates that their modulation can reprogram senescence phenotypes and thereby influence therapeutic sensitivity, highlighting their potential as both therapeutic targets and predictive biomarkers. However, their clinical implementation is currently limited by tumor heterogeneity, variability in senescence states and miRNA expression, insufficient delivery systems and carrier efficiency, off-target effects resulting from the pleiotropic nature of miRNAs, and the lack of standardized, universal biomarkers.

Future research should focus on combination strategies integrating SA-miRNA modulation with established therapeutic regimens, particularly chemotherapy, PARP inhibitors, and immunotherapy, in order to enhance response durability and reduce senescence-associated resistance. Advances in targeted delivery systems, including nanoparticles and biologically derived carriers, may improve both specificity and safety. In parallel, patient stratification based on miRNA profiling, along with the development of dynamic biomarkers, may support treatment mon-

itoring and prediction of therapeutic response. A deeper understanding of senescence heterogeneity, together with optimization of delivery platforms and well-designed early-phase clinical trials, will be critical for successful clinical translation. Collectively, these advances may enable the transition of SA-miRNAs from experimental regulators into clinically actionable components of precision oncology, particularly in therapy-resistant and recurrent ovarian cancer.

Author Contributions

JS conceptualized the review, conducted the literature search, performed data analysis, prepared all figures and tables, wrote the manuscript, and approved the final version for submission. JS has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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The author declares no conflicts of interest.

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