



Review Article

Online ISSN (3219-2789)

The Role of Non-Coding RNAs in Chemoresistance to Cancer Therapies

Ismail Ibrahim Al-Janabi* 

Retired Academic and Science Writer, Epsom, Surrey, United Kingdom

Received: 20 June 2026; Revised: 8 August 2026; Accepted: 18 August 2026

Abstract

Chemoresistance remains one of the greatest challenges in modern oncology and is responsible for most cancer-related deaths. Growing evidence has identified non-coding RNAs (ncRNAs) as key regulators of resistance to anticancer therapy. These molecules influence a wide range of classical resistance mechanisms, including drug efflux, apoptosis evasion, epithelial–mesenchymal transition, enhanced DNA repair, altered drug metabolism, and autophagy. The growing understanding of ncRNA biology has created new opportunities for clinical translation. Non-coding RNAs show considerable promise as predictive biomarkers of treatment response and as therapeutic targets, several of which have already entered early-phase clinical evaluation. Nevertheless, significant challenges remain, including the efficient and selective delivery, off-target effects, tumor heterogeneity, and redundancy in ncRNA regulatory networks.

Keywords: Cancer therapy; circRNAs; Drug resistance; lncRNAs; miRNAs; Non-coding RNAs.

دور الحامض النووي الريبوزي غير المشفر في مقاومة العلاجات الكيميائية للسرطان

الخلاصة

لا تزال مقاومة العلاج الكيميائي أحد أكبر التحديات في علم الأورام الحديث، وهي المسؤولة عن معظم الوفيات المرتبطة بالسرطان. وقد أشارت أدلة متزايدة إلى أن جزيئات الحامض النووي الريبوزي غير المشفر (ncRNAs) تُعد من أهم منظمات مقاومة العلاج المضاد للسرطان. تؤثر هذه الجزيئات على نطاق واسع من الآليات المقاومة التقليدية، بما في ذلك طرد الدواء، وتجنب موت الخلايا المبرمج، والتحول الظهاري-الميزانشيمي، وتعزيز إصلاح الحامض النووي، وتغيير استقلاب الدواء، والالتهام الذاتي. وقد أتاح الفهم المتزايد لبايولوجيا جزيئات الحامض النووي الريبوزي غير المشفر فرصًا جديدة للتطبيق السريري. يُظهر الحامض النووي الريبوزي غير المشفر إمكانات واعدة كمؤشرات حيوية تنبؤية للاستجابة للعلاج وأهداف علاجية، وقد دخل العديد منها بالفعل في المراحل المبكرة من التقييم السريري. ومع ذلك، لا تزال هناك تحديات كبيرة، بما في ذلك توصيل الفعال والانتقائي، والآثار الجانبية، وعدم تجانس الأورام، والتكرار في الشبكات التنظيمية لجزيئات الحامض النووي الريبوزي غير المشفر.

*Corresponding author: Ismail I. Al-Janabi. Retired Academic and Science Writer, Epsom, Surrey, United Kingdom; Email: ismail.janabi@gmail.com

Article citation: Al-Janabi II. The Role of Non-Coding RNAs in Chemoresistance to Cancer Therapies. *Al-Rafidain J Med Sci.* 2026;11(2):91-101. doi: <https://doi.org/10.54133/ajms.v11i2.3214>

© 2026 The Author(s). Published by Al-Rafidain University. This is an open access journal issued under the CC BY-NC-SA 4.0 license (<https://creativecommons.org/licenses/by-nc-sa/4.0/>).



INTRODUCTION

Cancer remains one of the most significant public health challenges of the 21st century. According to Global Cancer Observatory (GLOBOCAN) estimates for 2022, approximately 20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide [1]. Beyond its devastating impact on patients and families, cancer places an enormous economic burden on healthcare systems and societies, making it a major obstacle to sustainable global development [2]. Against this backdrop, systemic chemotherapy has remained a cornerstone of cancer treatment for more than eight decades [3]. Unlike localized approaches such as surgery and radiotherapy, chemotherapy can target disseminated tumor cells throughout the body, making it indispensable for the treatment of many hematological malignancies and advanced solid tumors and as both adjuvant and neoadjuvant therapy to reduce the risk of disease recurrence. Despite the emergence of innovative therapeutic modalities, including immunotherapy, chimeric antigen receptor T-cell (CAR-T) therapy, antibody–drug conjugates, and precision medicine guided by genomic profiling, chemotherapy continues

to play a central role in oncology [4-6]. In low- and middle-income countries, where access to newer therapies is often restricted by cost and infrastructure limitations, conventional chemotherapy accounts for most of the systemic cancer treatment [7-9]. Even in high-income countries, chemotherapy remains widely used in first-line, second-line, and palliative settings, frequently in combination with targeted therapies or immunotherapeutic agents [8]. However, the development of chemoresistance often undermines the effectiveness of chemotherapy, posing one of the most significant barriers to successful cancer treatment. Chemoresistance refers to the ability of cancer cells to survive and continue proliferating despite exposure to drug concentrations that would normally be sufficient to eliminate sensitive cells [10,11]. Clinically, resistance is typically recognized by disease progression during or following treatment, evidenced by increasing tumor burden, the emergence of new lesions, or worsening clinical symptoms. Based on its timing and underlying biology, chemoresistance is generally classified as either primary (intrinsic) resistance, in which tumors fail to respond to treatment from the outset, or acquired (secondary) resistance, which develops after an initial period of therapeutic

response [12]. The clinical consequences of chemoresistance are profound. It is estimated to contribute to most cancer-related deaths among patients receiving systemic therapy. In advanced solid tumors, five-year survival rates can decline dramatically when resistance emerges, falling from over 70% in treatment-sensitive disease to less than 15% in resistant tumors [13,14]. Beyond its impact on survival, chemoresistance exposes patients to prolonged courses of ineffective and often toxic therapies, resulting in increased morbidity, diminished quality of life, and substantial healthcare costs. Given the continued reliance on chemotherapy and the devastating consequences of treatment failure, understanding the molecular basis of chemoresistance remains a major research priority. Historically, investigations have focused on protein-coding genes and pathways, including oncogenes, tumor suppressor genes, and drug transporters. These protein-based mechanisms represent the direct effectors of resistance, ultimately determining whether a cancer cell survives or dies following chemotherapy. Several well-established mechanisms contribute to resistance, including increased drug efflux mediated by ATP-binding cassette (ABC) transporters, enzymatic inactivation of chemotherapeutic agents, genetic alterations in drug targets, enhanced DNA repair capacity, and dysregulation of apoptotic and pro-survival signalling pathways [15-20]. While these mechanisms remain critically important, the discovery that much of the human genome is transcribed into non-coding RNA has fundamentally transformed our understanding of gene regulation and cancer biology. Over the past decade, non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as key regulators of chemoresistance [21]. Unlike many protein-coding genes, these molecules can simultaneously influence multiple cellular pathways, including drug efflux, apoptosis, DNA repair, autophagy, metabolic reprogramming, and tumor-microenvironment interactions. Understanding the role of ncRNAs in chemoresistance extends far beyond academic interest. These molecules offer considerable potential as predictive biomarkers for treatment response, therapeutic targets for overcoming resistance, and tools for personalized cancer management. As such, elucidating the mechanisms by which ncRNAs regulate chemoresistance may ultimately lead to improved therapeutic outcomes for the millions of patients worldwide who continue to rely on chemotherapy. The subsequent sections of this review analyze the roles of the principal categories of ncRNAs in chemoresistance, investigate their prospective clinical applications, and address the obstacles that need to be overcome for these findings to be effectively integrated into standard patient care.

METHODS

A literature search was conducted covering publications from May 2006 to May 2026. Relevant

articles were identified using the keywords outlined above and by searching across several databases and search platforms, including PubMed, Google Scholar, Web of Science, and ResearchGate. The retrieved publications were screened by the author for relevance to the scope of this review. Study selection was informed by the scientific relevance of the articles, citation patterns within the literature, and the overall quality and impact of the publishing journals. Publications that were considered outside the scope of this narrative review were excluded. Although the primary search period was restricted to May 2006–May 2026, earlier publications were included where they provided important historical context or made a seminal contribution to the understanding of the topic.

Overview of ncRNAs in Cancer Biology

To understand the specific roles of ncRNAs in chemoresistance, it is essential to understand how they are produced and regulate gene expression and how their dysregulation contributes to cancer hallmarks. The focus in this overview will be on the three major ncRNA classes (microRNAs, long non-coding RNAs, and circular RNAs).

MicroRNAs

MicroRNAs (miRNAs) are small, single-stranded non-coding RNA molecules typically 19–25 nucleotides in length that play a central role in post-transcriptional gene regulation [22-24]. Most functional miRNAs are generated through the canonical biogenesis pathway, which begins with the transcription of miRNA genes by RNA polymerase II or, less commonly, RNA polymerase III, as illustrated in Figure 1.

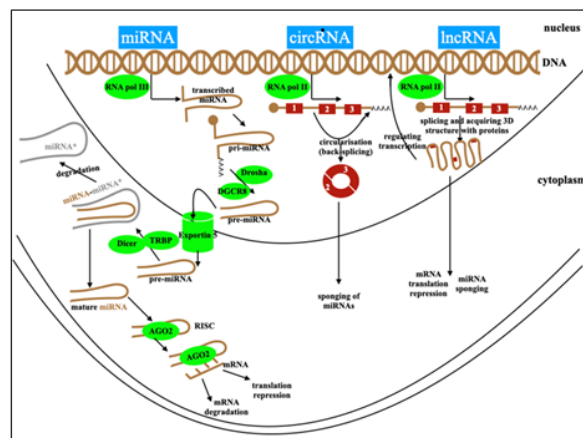


Figure 1: Biogenesis and regulatory mechanisms of microRNAs, circular RNAs, and long non-coding RNAs in cancer. Refer to the complete list of abbreviations at the end of the manuscript.

This process produces a primary miRNA transcript (pri-miRNA), a long RNA molecule containing a characteristic stem-loop (hairpin) structure as well as a 5' cap and a poly(A) tail. Within the nucleus, the pri-miRNA is recognized and processed by the microprocessor complex, which consists of the RNase III enzyme Drosha and its cofactor DGCR8 (DiGeorge syndrome critical region 8) [25]. This complex cleaves the hairpin region to generate a precursor miRNA (pre-miRNA), a ~70-nucleotide stem-loop structure

characterized by a two-nucleotide 3' overhang. The pre-miRNA is then exported from the nucleus to the cytoplasm by Exportin-5 (XPO5) (Figure 1). Once in the cytoplasm, the RNase III enzyme Dicer, together with accessory proteins such as TRBP or PACT, removes the terminal loop of the pre-miRNA to produce a double-stranded RNA duplex of approximately 22 nucleotides [26]. This duplex consists of a mature miRNA strand and a complementary passenger strand (miRNA*). The duplex is subsequently loaded onto an Argonaute (AGO) protein, predominantly AGO2 in humans, where strand selection occurs [27]. Generally, the strand with the less stable 5' end is retained as the guide strand, while the passenger strand is degraded. The mature miRNA-AGO complex forms the core of the RNA-induced silencing complex (RISC), which mediates gene silencing. The canonical function of miRNAs involves sequence-specific binding to complementary regions within target messenger RNAs (mRNAs), resulting in translational repression and/or mRNA degradation [25,28,29]. Through this mechanism, a single miRNA can regulate numerous target genes and influence a wide range of cellular processes. However, miRNAs are increasingly recognized to possess non-canonical functions as well [30]. These include the regulation of gene transcription, activation of toll-like receptors (TLRs), interaction with other non-coding RNAs through competitive binding, and association with proteins outside the Argonaute family (Figure 1). Dysregulation of miRNAs is a common feature of many cancers and can arise through multiple mechanisms, including genomic alterations, epigenetic silencing, defects in miRNA biogenesis, transcriptional deregulation, and disruption of competitive endogenous RNA (ceRNA) networks. Such alterations can profoundly affect tumor behavior, including responses to chemotherapy.

Circular RNAs

Circular RNAs (circRNAs) are a recently recognized class of non-coding RNAs (ncRNAs) distinguished by their covalently closed-loop structure, which lacks the 5' cap and 3' poly(A) tail characteristic of linear RNAs [31]. For many years, circRNAs were dismissed as rare splicing by-products or experimental artifacts. However, advances in high-throughput RNA sequencing and bioinformatics have revealed that circRNAs are abundant, evolutionarily conserved, and functionally important regulators of cellular processes. CircRNAs are generated from precursor messenger RNAs (pre-mRNAs) through a non-canonical splicing event known as back-splicing, in which a downstream splice donor site is covalently linked to an upstream splice acceptor site, resulting in the formation of a circular transcript [32,33] (Figure 1). Based on their composition, circRNAs can be broadly classified into three categories. Exonic circRNAs (ecircRNAs) are composed entirely of exons and represent the most abundant class. Circular intronic RNAs (ciRNAs) are derived exclusively from intronic sequences and are predominantly retained within the nucleus. Exon-

intron circRNAs (EiciRNAs) contain both exonic and intronic regions and often participate in transcriptional regulation [34]. One of the best-characterized functions of circRNAs is their ability to act as molecular "sponges" or decoys for microRNAs (miRNAs). Many circRNAs contain multiple binding sites for specific miRNAs, allowing them to sequester these molecules and prevent them from interacting with their target messenger RNAs [35]. Owing to their circular structure, circRNAs are highly resistant to degradation by the RNA-induced silencing complex (RISC), enabling sustained miRNA sequestration [36]. A classic example is ciRS-7 (CDR1as), which contains more than 70 conserved binding sites for miR-7 [37]. In cancers such as glioblastoma and colorectal cancer, overexpression of ciRS-7 suppresses miR-7 activity, leading to increased expression of oncogenic targets including EGFR, AKT, BCL2, and FAK, thereby promoting tumor growth and chemoresistance [38]. Beyond miRNA sponging, circRNAs can directly interact with proteins, either enhancing their activity or sequestering them away from their normal binding partners. For example, circANRIL binds to PES1, disrupting ribosome biogenesis and promoting apoptosis [39]. Although traditionally classified as non-coding RNAs, some circRNAs have also been shown to encode functional peptides through internal ribosome entry site (IRES)-mediated translation or N6-methyladenosine (m6A)-dependent cap-independent translation mechanisms [40]. Furthermore, nuclear-localized circRNAs, particularly EiciRNAs and ciRNAs, can regulate the transcription of their host genes through interactions with RNA polymerase II and U1 small nuclear ribonucleoprotein (U1 snRNP) [41]. Accumulating evidence suggests that circRNAs play a significant role in the development of chemoresistance. In many cases, this occurs through the sequestration of tumor-suppressive miRNAs [42]. Collectively, these findings highlight circRNAs as important regulators of cancer biology and therapeutic response. Their remarkable stability, tissue-specific expression patterns, and ability to modulate multiple resistance pathways make them promising biomarkers and potential therapeutic targets for overcoming chemoresistance.

Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are a diverse class of RNA transcripts with more than 200 nucleotides that possess little or no protein-coding capacity [43]. The human genome contains tens of thousands of lncRNA genes, with estimates ranging from approximately 20,000 to more than 100,000, potentially exceeding the number of protein-coding genes. Like messenger RNAs (mRNAs), most lncRNAs are transcribed by RNA polymerase II and undergo canonical RNA processing, including 5' capping, splicing, and polyadenylation [44]. Compared with mRNAs, lncRNAs are generally expressed at lower levels and often exhibit remarkable tissue-, cell type-, and developmental stage-specific expression patterns. They also tend to be less evolutionarily conserved than

protein-coding genes, reflecting their diverse and often context-dependent functions. Based on their genomic location relative to neighboring protein-coding genes, lncRNAs can be classified into several categories, including sense, antisense, intronic, intergenic, and bidirectional transcripts [43,44]. Unlike microRNAs, which primarily regulate gene expression through sequence-specific interactions with target mRNAs, lncRNAs exert their biological effects through a wide variety of molecular mechanisms [45]. These functions are often determined by their subcellular localization. Nuclear lncRNAs predominantly regulate gene expression at the transcriptional and epigenetic levels. They can influence chromatin architecture, recruit chromatin-remodelling complexes, modulate transcription factor activity, and regulate alternative splicing. Through these mechanisms, lncRNAs play important roles in controlling cellular identity, differentiation, and stress responses. In contrast, cytoplasmic lncRNAs are more commonly involved in post-transcriptional regulation [46]. Many act as competing endogenous RNAs (ceRNAs), sequestering microRNAs and preventing them from repressing their target genes. Others influence mRNA stability, regulate translation, or function as molecular scaffolds that facilitate the assembly of protein complexes and signalling pathways.

Mechanistic Pathways of ncRNA-Mediated Chemoresistance

This section examines the molecular mechanisms through which non-coding RNAs (ncRNAs) contribute to chemoresistance. Rather than acting as direct effectors of resistance, ncRNAs regulate the expression and activity of key proteins involved in a range of biological processes that ultimately determine therapeutic response. These processes include drug efflux, evasion of apoptosis, epithelial–mesenchymal transition (EMT), DNA damage repair, drug metabolism, and autophagy, diagrammatically shown in Figure 2.

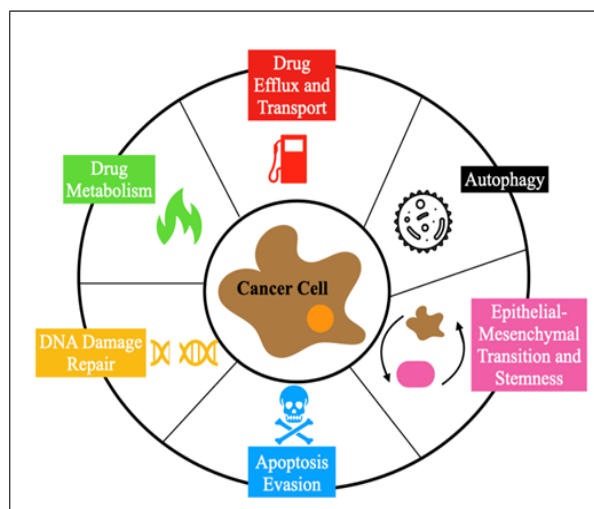


Figure 2: Mechanisms of chemoresistance in cancer. Non-coding RNAs (ncRNAs) regulate every classical resistance mechanism, and each pathway has multiple ncRNA regulators.

Drug efflux and drug transport

One of the best-characterized mechanisms of chemoresistance is the active removal of anticancer drugs from tumor cells by ATP-binding cassette (ABC) transporters [11,47]. These transmembrane proteins utilize energy derived from ATP hydrolysis to export a wide variety of chemotherapeutic agents, thereby reducing intracellular drug concentrations below cytotoxic levels. Among the large ABC transporter family, three members account for most clinically relevant multidrug resistance (MDR): ABCB1 (P-glycoprotein; P-gp), ABCC1 (multidrug resistance-associated protein 1; MRP1), and ABCG2 (breast cancer resistance protein; BCRP) [48]. Overexpression of these transporters is frequently observed in both intrinsic and acquired drug resistance. Emerging evidence indicates that ncRNAs act as key upstream regulators of ABC transporter expression at both the transcriptional and post-transcriptional levels [49]. MicroRNAs (miRNAs) play a particularly important role in controlling drug transporter expression. Numerous tumor-suppressive miRNAs directly bind to the 3' untranslated regions (3'UTRs) of ABC transporter mRNAs, promoting their degradation or inhibiting their translation [50]. Consequently, loss of these miRNAs is a common feature of chemoresistant cancers. For example, miR-27a and miR-451 directly target the 3'UTR of ABCB1 and modulate the PTEN/AKT signalling pathway [51]. In ovarian cancer, reduced miR-27a expression is associated with increased ABCB1 levels and resistance to paclitaxel, whereas restoration of miR-27a re-sensitizes tumor cells to treatment. Similarly, miR-145 directly suppresses both ABCB1 and ABCC1 expression in doxorubicin-resistant cancers, and the re-expression of miR-145 restores drug sensitivity [52–54]. Not all miRNAs regulate ABC transporters through direct binding. Some act indirectly by targeting transcription factors or signalling pathways that control transporter expression. The miR-200 family, particularly miR-200b and miR-200c, suppresses the transcription factors ZEB1 and ZEB2, which are central regulators of EMT. ZEB1 has also been shown to enhance ABCB1 transcription [55]. Consequently, loss of miR-200c leads to increased ZEB1 activity, elevated ABCB1 expression, and enhanced drug resistance. Reintroducing miR-200c reduces ABCB1 levels and restores paclitaxel sensitivity in ovarian cancer models [56]. Conversely, oncogenic miRNAs (oncomiRs) can promote resistance by activating signalling pathways that upregulate transporter expression. For instance, miR-21 suppresses PTEN, leading to activation of the AKT pathway and subsequent NF- κ B-mediated transcription of ABCB1 [57]. Circular RNAs (circRNAs) have also emerged as important regulators of drug efflux. Their covalently closed-loop structure renders them highly stable and particularly effective as miRNA sponges, allowing sustained derepression of ABC transporter expression. A well-characterized example is circPVT1, which sequesters the tumor-suppressive miRNAs miR-145-5p and miR-497-5p, both of which normally inhibit ABCB1 expression.

Elevated circPVT1 expression has been reported in drug-resistant gastric cancer cells, and its knockdown reduces ABCB1 levels while restoring sensitivity to doxorubicin [58]. Long non-coding RNAs (lncRNAs) regulate ABC transporters through several complementary mechanisms. Some function as competing endogenous RNAs (ceRNAs), sequestering miRNAs that would otherwise suppress transporter expression. For example, the lncRNA H19 acts as a sponge for members of the let-7 family, which normally target ABCB1 and ABCC1 transcripts. Increased H19 expression has been associated with ABCB1 overexpression and doxorubicin resistance in both breast and gastric cancers, whereas H19 silencing reduces transporter expression and enhances drug sensitivity [59].

Apoptosis evasion

The ability to evade apoptosis is one of the defining hallmarks of cancer and a major contributor to chemoresistance [11,60]. Most conventional chemotherapeutic agents exert their cytotoxic effects by inducing DNA damage, which activates the intrinsic (mitochondrial) apoptotic pathway. In response to DNA damage, the tumor suppressor protein TP53 promotes the transcription of pro-apoptotic members of the BCL2 family, including PUMA, NOXA, BAX, and BAK. These proteins trigger mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c into the cytoplasm. Cytochrome c subsequently activates caspase-9 and the downstream executioner caspases, particularly caspase-3, culminating in programmed cell death. Cancer cells frequently acquire resistance to chemotherapy by disrupting key components of this apoptotic machinery. Non-coding RNAs (ncRNAs) contribute to apoptosis evasion at virtually every stage of the pathway. These mechanisms include upregulation of anti-apoptotic proteins such as BCL2, BCL-XL, MCL-1, and BFL-1, suppression of pro-apoptotic BCL2 family members, inhibition of TP53 activity, and interference with caspase activation [61]. MicroRNAs (miRNAs) play a central role in regulating apoptotic signalling, with the balance between tumour-suppressive miRNAs and oncogenic miRNAs (oncomiRs) often determining whether a cell undergoes apoptosis or survives chemotherapy (Figure 3) [62]. Prominent tumor-suppressive miRNAs include miR-34a, miR-15a, members of the let-7 family, and the miR-200 family, all of which promote apoptosis by repressing genes involved in cell survival and proliferation. In contrast, oncomiRs such as miR-21, miR-155, and miR-221/222 enhance chemoresistance by suppressing tumor suppressor genes and activating pro-survival signaling pathways. Circular RNAs (circRNAs) influence apoptosis predominantly through their ability to function as miRNA sponges. A notable example is ciRS-7 (CDR1as), which sequesters miR-7, a microRNA that normally suppresses several oncogenic targets, including BCL2, EGFR, and AKT1 [63].

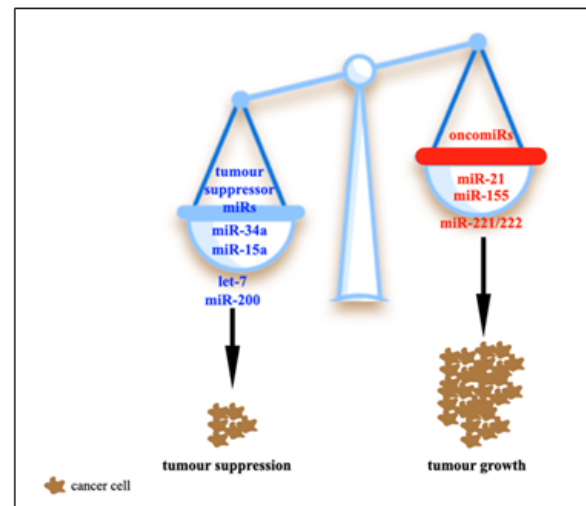


Figure 3: The influence of tumour suppressor microRNAs and oncogenic microRNAs (oncomiRs) on tumour suppression or growth. High levels of tumour suppressor microRNAs tip the balance in favour of tumour suppression.

Overexpression of ciRS-7, therefore, leads to increased expression of these pro-survival factors, promoting resistance to oxaliplatin and 5-fluorouracil (5-FU) in colorectal cancer. Long non-coding RNAs (lncRNAs) regulate apoptosis through a variety of interconnected mechanisms. Among the best-characterized examples is MALAT1, which promotes chemoresistance by enhancing survival signaling and suppressing apoptotic pathways [64]. MALAT1 can activate the AKT pathway through sequestration of miR-200 family members, thereby relieving repression of PTEN. It can also sponge miR-101, resulting in increased expression of the anti-apoptotic proteins MCL-1 and BCL2. MALAT1 has also been shown to interact directly with TP53, which keeps it in the cytoplasm and makes it less able to activate pro-apoptotic gene transcription.

Epithelial–mesenchymal transition (EMT) and cancer stemness

Epithelial–mesenchymal transition (EMT) is a cellular reprogramming process that enables epithelial cancer cells to acquire mesenchymal characteristics, including enhanced migratory capacity, invasiveness, and resistance to therapy. EMT is orchestrated by a network of master transcription factors, most notably ZEB1, ZEB2, SNAIL1, SNAIL2, TWIST1, TWIST2, and FOXC2, which collectively suppress epithelial traits and promote mesenchymal gene expression [65,66]. Cancer cells that undergo EMT often display a marked increase in chemoresistance through several complementary mechanisms [11,67]. These include reduced proliferative activity, which diminishes the effectiveness of chemotherapeutic agents that preferentially target rapidly dividing cells; increased expression of ATP-binding cassette (ABC) transporters that promote drug efflux; enhanced autophagy and anti-apoptotic signalling; and the acquisition of cancer stem cell (CSC)-like properties. The latter are particularly important, as CSCs possess self-renewal capacity and are frequently associated with tumor recurrence, metastasis, and resistance to multiple therapeutic modalities. Importantly, EMT is a

reversible process. Following the cessation of treatment, mesenchymal-like cells can undergo mesenchymal-to-epithelial transition (MET), re-establish proliferative tumor populations, and contribute to disease relapse [68]. Among the various non-coding RNAs involved in EMT regulation, the miR-200 family is widely regarded as a master suppressor of the EMT program [69]. Members of this family directly bind to the 3' untranslated regions of ZEB1 and ZEB2 transcripts, inhibiting their expression. Since ZEB1 and ZEB2 are potent transcriptional repressors of CDH1, the gene encoding E-cadherin, miR-200 expression helps maintain the epithelial phenotype. Loss of miR-200 family members is a common feature of aggressive and chemoresistant cancers and is frequently observed in circulating tumor cells (CTCs) from patients with advanced disease [70]. Notably, reduced miR-200 expression has been associated with poor response to chemotherapy and adverse clinical outcomes. Circular RNAs (circRNAs) can promote EMT by interfering with miRNA-mediated regulation of EMT transcription factors. A notable example is circ-ZEB1, which is generated from the ZEB1 genomic locus. Circ-ZEB1 functions as a sponge for members of the miR-200 family, thereby relieving repression of ZEB1 and establishing a positive feedback loop that further enhances EMT signalling [71]. Elevated circ-ZEB1 expression has been linked to increased invasiveness, chemoresistance, and poor prognosis in cancers such as glioblastoma and hepatocellular carcinoma. Long non-coding RNAs (lncRNAs) also play prominent roles in EMT-driven chemoresistance. MALAT1, mentioned earlier, promotes EMT through multiple interconnected mechanisms. MALAT1 can sequester members of the miR-200 family, particularly miR-200c, thereby facilitating ZEB1 and ZEB2 expression [72]. In addition, MALAT1 has been shown to enhance the expression of several key EMT-inducing transcription factors, including ZEB1, ZEB2, SNAIL, and TWIST1, through various signaling pathways. Functional studies have demonstrated that MALAT1 knockdown can reverse EMT, suppress invasive behavior, and restore sensitivity to chemotherapeutic agents such as gemcitabine in pancreatic cancer models [73,74].

DNA damage repair (DDR)

Many commonly used chemotherapeutic agents, including platinum compounds, alkylating agents, topoisomerase inhibitors, and anthracyclines, exert their anticancer effects by inducing DNA damage [4,18,75]. The effectiveness of these drugs depends largely on the inability of cancer cells to repair the resulting DNA lesions. To counteract this damage, cells employ several DNA damage repair (DDR) pathways, including nucleotide excision repair (NER), homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), and mismatch repair (MMR). Cancer cells frequently enhance the activity of these repair mechanisms, allowing them to survive chemotherapy-induced DNA damage. Non-coding RNAs (ncRNAs) have emerged

as important regulators of DDR, influencing repair processes at multiple molecular levels (Figure 4) [76].

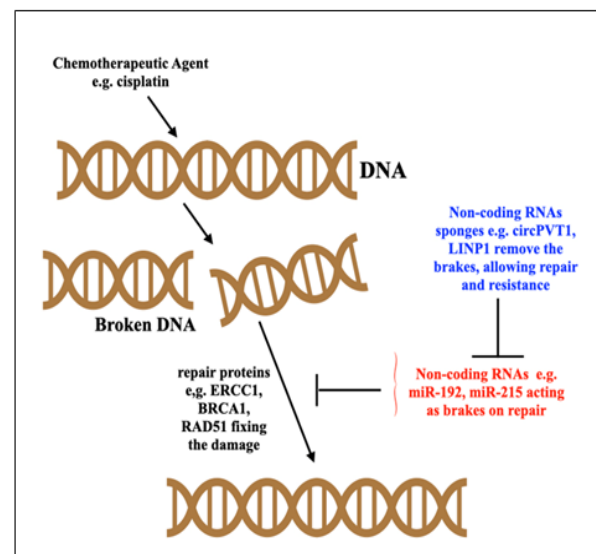


Figure 4: Non-coding RNA regulation of DNA damage response (DDR) pathways in chemoresistance. Non-coding RNAs regulate all major DDR pathways. Low tumour suppressor microRNAs allow enhanced DNA repair and resistance. Refer to the complete list of abbreviations at the end of the manuscript.

Among microRNAs, miR-192 and miR-215 are notable regulators of the NER pathway. Both directly target the 3' untranslated region of ERCC1, a key DNA repair protein involved in the removal of platinum-induced DNA adducts [77,78]. These microRNAs are induced by TP53 following DNA damage and act to suppress ERCC1 expression. Reduced levels of miR-192 and miR-215 have been associated with increased ERCC1 expression and poor responses to cisplatin therapy in non-small cell lung cancer (NSCLC) and ovarian cancer. Another important example is miR-9, which negatively regulates homologous recombination by directly targeting BRCA1 through binding to its 3'UTR, thereby reducing the cell's capacity to repair double-strand DNA breaks [79]. Circular RNAs (circRNAs) can also modulate DNA repair, although their mechanisms are not always based on miRNA sponging. A notable example is circFoxo3, which directly interacts with the DNA damage response kinases ATM and CHK2 [80]. Through these protein-protein interactions, circFoxo3 enhances DNA damage signalling and promotes HR repair. Silencing circFoxo3 reduces HR efficiency and restores sensitivity to doxorubicin in resistant breast cancer cells [81]. Importantly, this represents a protein-binding mechanism rather than the more commonly described miRNA sponge function of circRNAs. Long non-coding RNAs (lncRNAs) are similarly involved in regulating DDR pathways. NEAT1 promotes homologous recombination repair through interactions with epigenetic regulators such as EZH2 and by influencing the expression of RAD51, a central mediator of HR repair [82,83]. Elevated NEAT1 expression has been linked to cisplatin resistance in ovarian cancer [84,85].

Drug metabolism

Another important mechanism of chemoresistance involves alterations in drug metabolism. Cancer cells can increase the expression and activity of phase I and phase II drug-metabolizing enzymes, enabling them to detoxify or inactivate chemotherapeutic agents before they exert their cytotoxic effects [86,87]. Phase I reactions primarily involve oxidation and reduction processes, whereas phase II reactions help conjugate and eliminate drugs. Key enzyme families implicated in chemoresistance include the cytochrome P450 (CYP450) enzymes, particularly CYP1B1, CYP3A4, and CYP2C8, as well as glutathione S-transferases (GSTs), such as GST π and GST α , and uridine diphosphate glucuronosyltransferases (UGTs), including UGT1A1 and UGT2B7 [88,89]. MicroRNAs (miRNAs) play a major role in regulating the expression of these metabolic enzymes. For example, miR-27b directly targets CYP1B1, and loss of miR-27b expression in breast cancer leads to increased CYP1B1 levels, enhanced docetaxel metabolism, and reduced drug efficacy [90]. Similarly, miR-148a negatively regulates CYP3A4, one of the most important drug-metabolizing enzymes in humans [91]. Downregulation of miR-148a in liver cancer has been associated with elevated CYP3A4 expression and diminished responsiveness to irinotecan [92,93]. Compared with miRNAs and lncRNAs, relatively little is currently known about the role of circular RNAs (circRNAs) in regulating drug metabolism. Nevertheless, emerging evidence suggests that circRNAs may indirectly influence the expression of metabolic enzymes by acting as sponges for miRNAs that normally suppress these targets [94-96]. This remains an active area of investigation, and further studies are needed to clarify the contribution of circRNAs to metabolism-driven chemoresistance. Long non-coding RNAs (lncRNAs) have also been implicated in the regulation of drug-metabolizing enzymes through a variety of mechanisms. The lncRNA H19, for example, has been shown to influence CYP3A4 transcription through interactions with transcriptional regulatory proteins, a mechanism that may contribute to methotrexate resistance [97]. Another lncRNA, HCP5, promotes chemoresistance by both stabilizing CYP1B1 mRNA and sponging miR-3619-5p, a microRNA that normally suppresses GST π expression [98,99]. Elevated HCP5 levels have been reported in platinum-resistant ovarian cancer, supporting its role in drug detoxification and treatment failure [100].

Autophagy

Autophagy is an evolutionarily conserved lysosomal degradation pathway that enables cells to recycle damaged organelles, proteins, and other intracellular components under conditions of stress. In cancer, autophagy plays a complex and context-dependent role, functioning as either a survival mechanism or a cell death pathway [101]. In its cytoprotective form, autophagy promotes tumor cell survival by removing damaged cellular components, reducing oxidative

stress, and providing metabolic substrates during periods of nutrient deprivation or therapeutic stress. Conversely, excessive or sustained autophagy can contribute to cell death. In the setting of chemoresistance, however, cytoprotective autophagy is most observed and is frequently upregulated in response to anticancer treatment. Several key proteins regulate the autophagic process, including Beclin-1 (BECN1), LC3-II (microtubule-associated protein 1 light chain 3-II), ULK1, and a range of autophagy-related genes (ATGs) [102]. Numerous chemotherapeutic agents have been shown to induce cytoprotective autophagy, including platinum compounds, taxanes, tyrosine kinase inhibitors, PARP inhibitors, and antimetabolites. Activation of this pathway can allow cancer cells to withstand treatment-induced stress, thereby contributing to therapeutic resistance. MicroRNAs (miRNAs) are important regulators of autophagy and exert their effects by targeting autophagy-related genes, key autophagy proteins, and upstream signalling pathways such as AMPK and mTOR. Depending on the specific targets involved, miRNAs can either suppress autophagy and restore drug sensitivity or enhance autophagy and promote resistance. One well-characterized example is miR-30a, which directly targets the 3' untranslated regions of BECN1 and ATG5, thereby reducing autophagosome formation [103]. Overexpression of miR-30a decreases Beclin-1 expression, inhibits autophagy, and resensitizes ovarian cancer cells to cisplatin. In contrast, miR-21 promotes chemoresistance by suppressing PTEN, leading to activation of the PI3K/AKT signalling pathway and enhanced survival of pancreatic cancer cells exposed to gemcitabine [104]. MiR-21 can also suppress TSC1, a negative regulator of mTOR, highlighting the complex and context-dependent nature of miRNA-mediated autophagy regulation [105]. Circular RNAs (circRNAs) influence autophagy primarily through their ability to function as miRNA sponges. For example, circPVT1 promotes autophagy by sequestering miR-145-5p and miR-497-5p, which normally suppress ATG14 and ATG7, respectively. Increased circPVT1 expression has been associated with enhanced autophagic activity and cisplatin resistance in gastric cancer (see Figure 5 depicting the involvement of this circular RNA as a part of a competing endogenous RNA, ceRNA, network) [58,106]. Long non-coding RNAs (lncRNAs) regulate autophagy through a variety of mechanisms, including miRNA sponging, protein scaffolding, and modulation of signaling pathways. MALAT1, which promotes cytoprotective autophagy through several complementary mechanisms, can sponge miR-101, thereby increasing expression of ATG4D and miR-30a, resulting in elevated Beclin-1 levels [107]. In addition, MALAT1 has been reported to interact directly with and stabilize autophagy-related proteins such as LC3 and Beclin-1, further enhancing autophagic flux. In contrast, the lncRNA GAS5 functions as a negative regulator of autophagy. GAS5 suppresses autophagy primarily by sponging miR-21, thereby counteracting

one of the major pro-autophagic pathways involved in chemoresistance [108].

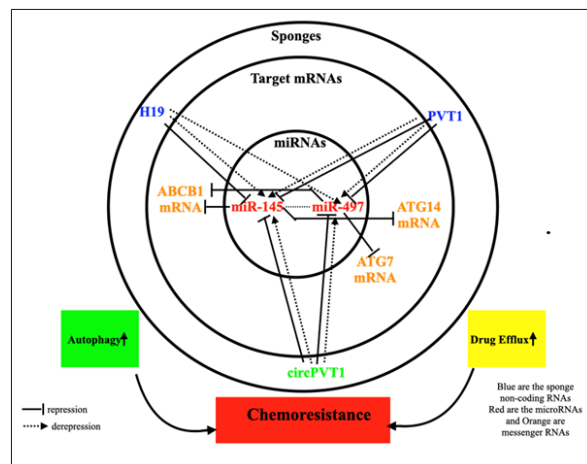


Figure 5: An example of competing endogenous RNA (ceRNA) network orchestrating chemoresistance and illustrating the possible complexity of interactions involved. In resistant cells, H19, PVT1, and circPVT1 are upregulated. They sponge miR-145 and miR-497, derepressing ABCB1 (drug efflux) and ATG7/ATG14 (cytoprotective autophagy) prompting chemoresistance. Restoring miR-145/miR-497 or targeting H19/PVT1/circPVT1 resensitises cells to doxorubicin and cisplatin. The complete list of abbreviations is available at the end of the manuscript.

Reduced GAS5 expression has been observed in cisplatin-resistant ovarian cancer, whereas the restoration of GAS5 expression inhibits autophagy and resensitizes tumor cells to chemotherapy.

Conclusions

The recognition of non-coding RNAs as key regulators of chemoresistance has significantly advanced our understanding of how cancer cells adapt to therapeutic pressure. Instead of just being by-products of gene expression, ncRNAs are involved in controlling many resistance mechanisms, such as drug efflux, avoiding apoptosis, epithelial–mesenchymal transition, repairing DNA damage, changing drug metabolism, and autophagy. Through their extensive and interconnected regulatory networks, ncRNAs influence both intrinsic and acquired resistance across a wide range of malignancies. The growing body of evidence reviewed here demonstrates the potential of ncRNAs not only as mechanistic drivers of chemoresistance but also as promising biomarkers for predicting treatment response and disease progression. Furthermore, therapeutic approaches targeting ncRNA networks offer new opportunities to overcome resistance and enhance the effectiveness of existing anticancer therapies. Despite these advances, several challenges continue to limit clinical translation. The complexity and context-dependent nature of ncRNA signaling, tumor heterogeneity, network redundancy, and the difficulties associated with efficient and selective delivery remain significant obstacles. Addressing these issues will require the integration of emerging technologies, including single-cell transcriptomics, advanced RNA delivery platforms, liquid biopsy approaches, and artificial intelligence-assisted network analysis. As our understanding of ncRNA biology

continues to evolve, it is becoming increasingly clear that these molecules occupy a central position in the molecular landscape of chemoresistance. Continued investigation of ncRNA regulatory networks is likely to provide valuable insights into cancer biology and may ultimately lead to more precise and effective therapeutic strategies for patients with treatment-resistant diseases.

Abbreviations

5-FU: 5-fluorouracil; ABC: ATP-binding cassette; AGO: Argonaute protein; AKT: protein kinase also known as PKB; AMPK: AMP-activated protein kinase; ATGs: autophagy-related genes; BAX: BCL2-associated X protein; BCL-XL: B cell lymphoma-extra-large; BCL2: B cell leukemia/lymphoma 2; BCRP: breast cancer resistance protein or ABCG2; BECN1: Beclin-1; BER: base excision repair; BFL-1: BCL-related protein A1; BRCA: breast cancer protein/gene; CAR-T: chimeric antigen receptor T-cell; ceRNA: competitive endogenous RNA; CHK2: checkpoint kinase 2; circRNAs: circular RNAs; ciRNAs: circular intronic RNAs; CSC: cancer stem cell; CTCs: circulating tumor cells; CYP450: cytochrome p450 (massive and diverse superfamily of enzymes); DDR: DNA damage repair; ecircRNAs: exonic circular RNAs; EGFR: epidermal growth factor receptor; EiCiRNAs: exon-intron circular RNAs; EMT: epithelial-mesenchymal transition; ERCC1: excision repair cross-complement group 1; EZH2: enhancer of zeste homolog 2; FAK: focal adhesion kinase; FOXO2: forkhead box C2; GSTs: glutathione-S-transferases; HR: homologous recombination; IRES: internal ribosome entry site; LC3-II microtubule-associated protein 1 light chain 3-II; LINP1: lncRNA in non-homologous end joining pathway; lncRNAs: long non-coding RNAs; MALAT1: lncRNA-metastasis-associated lung adenocarcinoma transcript 1; MCL-1: myeloid cell leukemia sequence 1; MDR: multidrug resistance; MET: mesenchymal-epithelial transition; miRNAs: microRNAs; MMR: mismatch repair; MOMP: mitochondrial outer membrane permeabilization; mRNA: messenger RNA; MRP1: a member of MDR protein or ABCG1; mTOR: mechanistic target of rapamycin; ncRNAs: non-coding RNAs; NEAT1: nuclear paraspeckle assembly transcript 1; NER: nucleotide excision repair; NHEJ: non-homologous end joining; NOXA: pro-apoptosis protein; NSCLC: non-small cell lung cancer; P-gp: P-glycoprotein or ABCB1; PACT: protein activator of the interferon-induced protein kinase cellular translation; PARP: poly (ADP-ribose) polymerase; PES1: pescadillo ribosomal biogenesis factor; PI3K: phosphatidylinositol-3-kinase; pre-miRNA: precursor miRNA; pri-miRNA: primary miRNA; PTEN: phosphatase and tensin; PUMA: p53 upregulated modulator of apoptosis; PVT1: lncRNA plasmacytoma variant translocation; RAD51: radiation-sensitive 51; RISC: RNA-induced silencing complex; SNAIL 1 and 2: snail family transcriptional repressors 1 and 2; snRNP: small nuclear ribonucleoprotein; TLRs: toll-like receptors; TP53: tumor protein 53; TRBP: trans-

activation responsive RNA-binding protein; TSC1: tuberous sclerosis complex 1; TWIST1 and 2: twist-related protein 1 and 2; UGTs: uridine diphosphate glucuronosyltransferases; ULK1: unc-51-like autophagy activating kinase 1; UTR: untranslated region; XPO5: Exportin-5; ZEB1 and 2: zinc finger E-box binding homeobox 1 and 2.

ACKNOWLEDGMENTS

The author is grateful for the help and support received from Mrs. Joanna S. Al-Janabi in the preparation of this manuscript.

Conflict of interests

The author declared no conflict of interest.

Funding source

The author did not receive any source of funds.

Data sharing statement

N/A.

REFERENCES

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi: 10.3322/caac.21834.
- Chen S, Cao Z, Prettnier K, Kuhn M, Yang J, Jiao L, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. *JAMA Oncol*. 2023;9(4):465. doi: 10.1001/jamaoncol.2022.7826.
- DeVita VT, Chu E. A history of cancer chemotherapy. *Cancer Res*. 2008;68(21):8643–8653. doi: 10.1158/0008-5472.can-07-6611.
- Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes Dis*. 2023;10(4):1367–1401. doi: 10.1016/j.gendis.2022.02.007.
- Zhang WY, Yang LY, Fan XX. CAR-T therapy-based innovations in the enhancement of contemporary anti-tumor therapies. *Front Immunol*. 2025;16. doi: 10.3389/fimmu.2025.1622433.
- Kale E, Guzes E, Alatas F, Sharafi P. Next-generation cancer therapies: translating experimental advances into clinical practice. *Postgrad Med J*. 2026;102(1208):497–510. doi: 10.1093/postmj/qgaf242.
- Tfayli AH, El-Halabi LN, Khuri FR. Global disparities in cancer care: Bridging the gap in affordability and access to medications between high and low-income countries. *Cancer*. 2024;131(1). doi: 10.1002/cncr.35590.
- Hofmarcher T, Charalambous A, Normanno N, Szmytke E, Wilking N. Access to novel cancer medicines in Europe: inequities across countries and their drivers. *ESMO Open*. 2025;10(10):105810. doi: 10.1016/j.esmoop.2025.105810.
- Ruge L, Verheyen M, John F, Wolf J. Global disparities in access to diagnostics and therapies for advanced non-small cell lung cancer: from discovery to delivery – a review. *Front Oncol*. 2026;16. doi: 10.3389/fonc.2026.1807704.
- Rezayatmand H, Razmkhah M, Razeghian-Jahromi I. Drug resistance in cancer therapy: the Pandora's Box of cancer stem cells. *Stem Cell Res Ther*. 2022;13(1). doi: 10.1186/s13287-022-02856-6.
- Dhiman VK, Kumari M, Singh D. Chemoresistance: The hidden barrier in cancer treatment. *Cancer Pathogenesis Ther*. 2026;4(2):98–109. doi: 10.1016/j.cpt.2025.07.001.
- Cetin R, Quandt E, Kaulich M. Functional genomics approaches to elucidate vulnerabilities of intrinsic and acquired chemotherapy resistance. *Cells*. 2021;10(2):260. doi: 10.3390/cells10020260.
- Wang Q, Shen X, Chen G, Du J. Drug resistance in colorectal cancer: From mechanism to clinic. *Cancers (Basel)*. 2022;14(12):2928. doi: 10.3390/cancers14122928.
- Mo J, Zaremba A, Inderjeeth AJ, el Zeinaty P, Li A, Wicky A, et al. Clinical outcomes and management following progressive disease with anti-PD-(L)1 therapy in patients with advanced Merkel Cell Carcinoma. *Eur J Cancer*. 2025;217:115254. doi: 10.1016/j.ejca.2025.115254.
- Sun D, Bo L, Jiang C, Lan Y, Zhang B, Zhang C, et al. Beyond the boundary: The emerging roles of ATP-binding cassette transporters in multidrug resistance (MDR) and therapeutic targeting in cancer. *Drug Resist Updates*. 2026;84:101310. doi: 10.1016/j.drug.2025.101310.
- Fulda S. Evasion of apoptosis as a cellular stress response in cancer. *Int J Cell Biol*. 2010;2010:1–6. doi: 10.1155/2010/370835.
- Dart A. EMT in chemoresistance. *Nat Rev Cancer*. 2023;23(6):349–349. doi: 10.1038/s41568-023-00581-7.
- Nesic K, Parker P, Swisher EM, Krais JJ. DNA repair and the contribution to chemotherapy resistance. *Genome Med*. 2025;17(1). doi: 10.1186/s13073-025-01488-8.
- Chen X, Chen S, Yu D. Metabolic reprogramming of chemoresistant cancer cells and the potential significance of metabolic regulation in the reversal of cancer chemoresistance. *Metabolites*. 2020;10(7):289. doi: 10.3390/metabo10070289.
- Li X, Zhou Y, Li Y, Yang L, Ma Y, Peng X, et al. Autophagy: A novel mechanism of chemoresistance in cancers. *Biomed Pharmacother*. 2019;119:109415. doi: 10.1016/j.biopha.2019.109415.
- Zhou X, Ao X, Jia Z, Li Y, Kuang S, Du C, et al. Non-coding RNA in cancer drug resistance: Underlying mechanisms and clinical applications. *Front Oncol*. 2022;12. doi: 10.3389/fonc.2022.951864.
- Bartel DP. MicroRNAs. *Cell*. 2004;116(2):281–297. doi: 10.1016/s0092-8674(04)00045-5.
- Peng Y, Croce CM. The role of MicroRNAs in human cancer. *Signal Transduct Target Ther*. 2016;1(1). doi: 10.1038/sigtrans.2015.4.
- Dexheimer PJ, Cochella L. MicroRNAs: From mechanism to organism. *Front Cell Dev Biol*. 2020;8. doi: 10.3389/fcell.2020.00409.
- Han J, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN. The Drosha-DGCR8 complex in primary microRNA processing. *Genes Dev*. 2004;18(24):3016–3027. doi: 10.1101/gad.1262504.
- Vergani-Junior CA, Tonon-da-Silva G, Inan MD, Mori MA. DICER: structure, function, and regulation. *Biophys Rev*. 2021;13(6):1081–1090. doi: 10.1007/s12551-021-00902-w.
- Dueck A, Ziegler C, Eichner A, Berezikov E, Meister G. microRNAs associated with the different human Argonaute proteins. *Nucleic Acids Res*. 2012;40(19):9850–9862. doi: 10.1093/nar/gks705.
- Pekarek L, Torres-Carranza D, Fraile-Martinez O, García-Montero C, Pekarek T, Saez MA, et al. An overview of the role of microRNAs on carcinogenesis: A focus on cell cycle, angiogenesis and metastasis. *Int J Mol Sci*. 2023;24(8):7268. doi: 10.3390/ijms24087268.
- Ding S, Wang P. The life of microRNAs: Biogenesis, function and decay in cancer. *Biomolecules*. 2025;15(10):1393. doi: 10.3390/biom15101393.
- Dragomir MP, Knutsen E, Calin GA. Classical and noncanonical functions of miRNAs in cancers. *Trend Genet*. 2022;38(4):379–394. doi: 10.1016/j.tig.2021.10.002.
- Conn VM, Chinnaiyan AM, Conn SJ. Circular RNA in cancer. *Nat Rev Cancer*. 2024;24(9):597–613. doi: 10.1038/s41568-024-00721-7.
- Hussen BM, Abdullah SR, Jaafar RM, Rasul MF, Aroutiounian R, Harutyunyan T, et al. Circular RNAs as key regulators in cancer hallmarks: New progress and therapeutic opportunities. *Crit Rev Oncol Hematol*. 2025;207:104612. doi: 10.1016/j.critrevonc.2024.104612.
- Guo Y, Huang Q, Heng Y, Zhou Y, Chen H, Xu C, et al. Circular RNAs in cancer. *MedComm (Beijing)*. 2025;6(2). doi: 10.1002/mco2.70079.

34. Shafaghat Z, Radmehr S, Saharkhiz S, Khosrozadeh A, Feiz K, Alkhathami AG, et al. Circular RNA, a molecule with potential chemistry and applications in RNA-based cancer therapeutics: An insight into recent advances. *Top Curr Chem.* 2025;383(2). doi: 10.1007/s41061-025-00505-z.
35. Kumar L, Shamsuzzama, Haque R, Baghel T, Nazir A. Circular RNAs: The emerging class of non-coding RNAs and their potential role in human neurodegenerative diseases. *Mol Neurobiol.* 2016;54(9):7224–7234. doi: 10.1007/s12035-016-0213-8.
36. Sakshi S, Jayasuriya R, Ganesan K, Xu B, Ramkumar KM. Role of circRNA-miRNA-mRNA interaction network in diabetes and its associated complications. *Mol Ther Nucleic Acids.* 2021;26:1291–302. doi: 10.1016/j.omtn.2021.11.007.
37. Guo Z, Cao Q, Zhao Z, Song C. Biogenesis, features, functions, and disease relationships of a specific circular RNA: CDR1as. *Aging Dis.* 2020;11(4):1009. doi: 10.14336/ad.2019.0920.
38. Chen J, Yang J, Fei X, Wang X, Wang K. CircRNA ciRS-7: A novel oncogene in multiple cancers. *Int J Biol Sci.* 2021;17(1):379–389. doi: 10.7150/ijbs.54292.
39. Holdt LM, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun.* 2016;7(1). doi: 10.1038/ncomms12429.
40. He L, Man C, Xiang S, Yao L, Wang X, Fan Y. Circular RNAs' cap-independent translation protein and its roles in carcinomas. *Mol Cancer.* 2021;20(1). doi: 10.1186/s12943-021-01417-4.
41. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. *Mol Cancer.* 2020;19(1). doi: 10.1186/s12943-020-01286-3.
42. Hashemi M, Khosroshahi EM, Daneii P, Hassanpoor A, Eslami M, Koohpar ZK, et al. Emerging roles of CircRNA-miRNA networks in cancer development and therapeutic response. *Noncoding RNA Res.* 2025;10:98–115. doi: 10.1016/j.ncrna.2024.09.006.
43. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. *Nat Rev Mol Cell Biol.* 2023;24(6):430–447. doi: 10.1038/s41580-022-00566-8.
44. Zhang X, Wang W, Zhu W, Dong J, Cheng Y, Yin Z, et al. Mechanisms and functions of long non-coding RNAs at multiple regulatory levels. *Int J Mol Sci.* 2019;20(22):5573. doi: 10.3390/ijms20225573.
45. Hu G, Niu F, Humburg BA, Liao K, Bendi S, Callen S, et al. Molecular mechanisms of long noncoding RNAs and their role in disease pathogenesis. *Oncotarget.* 2018;9(26):18648–18663. doi: 10.18632/oncotarget.24307.
46. Noh JH, Kim KM, McClusky WG, Abdelmohsen K, Gorospe M. Cytoplasmic functions of long noncoding RNAs. *WIREs RNA.* 2018;9(3). doi: 10.1002/wrna.1471.
47. Begicevic RR, Falasca M. ABC Transporters in cancer stem cells: Beyond chemoresistance. *Int J Mol Sci.* 2017;18(11):2362. doi: 10.3390/ijms18112362.
48. Huang J, Ecker GF. A structure-based view on ABC-transporter linked to multidrug resistance. *Molecules.* 2023;28(2):495. doi: 10.3390/molecules28020495.
49. Ebrahimnezhad M, Asl SH, Rezaie M, Molavand M, Yousefi B, Majidinia M. lncRNAs: New players of cancer drug resistance via targeting ABC transporters. *IUBMB Life.* 2024;76(11):883–921. doi: 10.1002/iub.2888.
50. Haenisch S, Werk AN, Cascorbi I. MicroRNAs and their relevance to ABC transporters. *Br J Clin Pharmacol.* 2014;77(4):587–596. doi: 10.1111/bcp.12251.
51. Zhu H, Wu H, Liu X, Evans BR, Medina DJ, Liu CG, et al. Role of microRNA miR-27a and miR-451 in the regulation of MDR1/p-glycoprotein expression in human cancer cells. *Biochem Pharmacol.* 2008;76(5):582–588. doi: 10.1016/j.bcp.2008.06.007.
52. Li G, Gong J, Cao S, Wu Z, Cheng D, Zhu J, et al. The non-coding RNAs inducing drug resistance in ovarian cancer: A new perspective for understanding drug resistance. *Front Oncol.* 2021;11. doi: 10.3389/fonc.2021.742149.
53. Ghafouri-Fard S, Shoorai H, Abak A, Abbas Raza SH, Pichler M, Taheri M. Role of non-coding RNAs in modulating the response of cancer cells to paclitaxel treatment. *Biomed Pharmacother.* 2021;134:111172. doi: 10.1016/j.biopha.2020.111172.
54. Gao M, Miao L, Liu M, Li C, Yu C, Yan H, et al. miR-145 sensitizes breast cancer to doxorubicin by targeting multidrug resistance-associated protein-1. *Oncotarget.* 2016;7(37):59714–59726. doi: 10.18632/oncotarget.10845.
55. Bendoraite A, Knouf EC, Garg KS, Parkin RK, Kroh EM, O'Brian KC, et al. Regulation of miR-200 family microRNAs and ZEB transcription factors in ovarian cancer: Evidence supporting a mesothelial-to-epithelial transition. *Gynecol Oncol.* 2010;116(1):117–125. doi: 10.1016/j.ygyno.2009.08.009.
56. Cittelly DM, Dimitrova I, Howe EN, Cochrane DR, Jean A, Spoelstra NS, et al. Restoration of miR-200c to ovarian cancer reduces tumor burden and increases sensitivity to paclitaxel. *Mol Cancer Ther.* 2012;11(12):2556–2565. doi: 10.1158/1535-7163.mct-12-0463.
57. Chawra HS, Agarwal M, Mishra A, Chandel SS, Singh RP, Dubey G, et al. MicroRNA-21's role in PTEN suppression and PI3K/AKT activation: Implications for cancer biology. *Pathol Res Pract.* 2024;254:155091. doi: 10.1016/j.prp.2024.155091.
58. Ghafouri-Fard S, Khoshbakht T, Taheri M, Jamali E. A concise review on the role of circPVT1 in tumorigenesis, drug sensitivity, and cancer prognosis. *Front Oncol.* 2021;11. doi: 10.3389/fonc.2021.762960.
59. Zhang X, Luo M, Zhang J, Guo B, Singh S, Lin X, et al. The role of lncRNA H19 in tumorigenesis and drug resistance of human cancers. *Front Genet.* 2022;13. doi: 10.3389/fgene.2022.1005522.
60. Al-Janabi I. Manipulating Cell Death in Cancer. *Al-Rafidain J Med Sci.* 2025;9(1):63–73. doi: 10.54133/ajms.v9i1.2131.
61. Villanova L, Careccia S, de Maria R, Fiori M. Microeconomics of apoptosis in cancer: ncRNAs modulation of BCL-2 family members. *Int J Mol Sci.* 2018;19(4):958. doi: 10.3390/ijms19040958.
62. Svoronos AA, Engelman DM, Slack FJ. OncomiR or tumor suppressor? The duplicity of microRNAs in cancer. *Cancer Res.* 2016;76(13):3666–3670. doi: 10.1158/0008-5472.can-16-0359.
63. Rahmati Y, Asemani Y, Aghamiri S, Ezzatifar F, Najafi S. CiRS-7/CDR1as: An oncogenic circular RNA as a potential cancer biomarker. *Pathol Res Pract.* 2021;227:153639. doi: 10.1016/j.prp.2021.153639.
64. Hou J, Zhang G, Wang X, Wang Y, Wang K. Functions and mechanisms of lncRNA MALAT1 in cancer chemotherapy resistance. *Biomark Res.* 2023;11(1). doi: 10.1186/s40364-023-00467-8.
65. Ribatti D, Tamma R, Annese T. Epithelial-mesenchymal transition in cancer: A historical overview. *Transl Oncol.* 2020;13(6):100773. doi: 10.1016/j.tranon.2020.100773.
66. Al-Janabi I. Epithelial-mesenchymal transition and tumour progression: An overview. *Al-Rafidain J Med Sci.* 2023;4:6–21. doi: 10.54133/ajms.v4i.99.
67. Du B, Shim J. Targeting epithelial–mesenchymal transition (EMT) to overcome drug resistance in cancer. *Molecules.* 2016;21(7):965. doi: 10.3390/molecules21070965.
68. Ghorbian S. Cancer cell plasticity and therapeutic resistance: mechanisms, crosstalk, and translational perspectives. *Hereditas.* 2025;162(1). doi: 10.1186/s41065-025-00564-8.
69. Korpai M, Kang Y. The emerging role of miR-200 family of MicroRNAs in epithelial-mesenchymal transition and cancer metastasis. *RNA Biol.* 2008;5(3):115–119. doi: 10.4161/rna.5.3.6558.
70. Liu J, Du H, Shi Y. Role and underlying mechanisms of miR-200 family in breast cancer (Review). *Int J Oncol.* 2026;68(4):1–18. doi: 10.3892/ijo.2026.5856.
71. Ashrafizadeh M, Ang HL, Moghadam ER, Mohammadi S, Zarrin V, Hushmandi K, et al. MicroRNAs and their influence on the ZEB family: Mechanistic aspects and therapeutic applications in cancer therapy. *Biomolecules.* 2020;10(7):1040. doi: 10.3390/biom10071040.
72. Matuszyk J. Circular RNA MALAT1 as a potential target for antimetastatic therapy. *Noncoding RNA Res.* 2026;17:12–20. doi: 10.1016/j.ncrna.2025.11.004.
73. Hussein MA, Valinezhad K, Adel E, Munirathinam G. MALAT-1 is a key regulator of epithelial–mesenchymal transition in cancer: A potential therapeutic target for metastasis. *Cancers (Basel).* 2024;16(1):234. doi: 10.3390/cancers16010234.

74. Jiao F, Hu H, Han T, Yuan C, Wang L, Jin Z, et al. Long noncoding RNA MALAT-1 enhances stem cell-like phenotypes in pancreatic cancer cells. *Int J Mol Sci.* 2015;16(4):6677–6693. doi: 10.3390/ijms16046677.
75. van den Boogaard WMC, Komninos DSJ, Vermeij WP. Chemotherapy side-effects: Not all DNA damage is equal. *Cancers (Basel).* 2022;14(3):627. doi: 10.3390/cancers14030627.
76. Moon J, Kitty I, Renata K, Qin S, Zhao F, Kim W. DNA damage and its role in cancer therapeutics. *Int J Mol Sci.* 2023;24(5):4741. doi: 10.3390/ijms24054741.
77. Zhou J, Kang Y, Chen L, Wang H, Liu J, Zeng S, et al. The drug-resistance mechanisms of five platinum-based antitumor agents. *Front Pharmacol.* 2020;11. doi: 10.3389/fphar.2020.00343.
78. Xie X, Huang N, Zhang Y, Wei X, Gao M, Li M, et al. MiR-192-5p reverses cisplatin resistance by targeting ERCC3 and ERCC4 in SGC7901/DDP cells. *J Cancer.* 2019;10(4):1039–1051. doi: 10.7150/jca.25814.
79. Sun C, Li N, Yang Z, Zhou B, He Y, Weng D, et al. miR-9 regulation of BRCA1 and ovarian cancer sensitivity to cisplatin and PARP inhibition. *JNCI: J Natl Cancer Instit.* 2013;105(22):1750–1758. doi: 10.1093/jnci/djt302.
80. Chung YM, Park SH, Tsai WB, Wang SY, Ikeda MA, Berek JS, et al. FOXO3 signalling links ATM to the p53 apoptotic pathway following DNA damage. *Nat Commun.* 2012;3(1). doi: 10.1038/ncomms2008.
81. Kamalabadi-Farahani M, Atashi A, Eslami MM. Downregulation of circ-Foxo3 in breast cancer stem-like cells. *BMC Res Notes.* 2023;16(1). doi: 10.1186/s13104-023-06405-z.
82. Long F, Li X, Pan J, Ye H, Di C, Huang Y, et al. The role of lncRNA NEAT1 in human cancer chemoresistance. *Cancer Cell Int.* 2024;24(1). doi: 10.1186/s12935-024-03426-x.
83. Xu W, Wu Y, Zhang G. NEAT1 promotes the progression of prostate cancer by targeting the miR-582-5p/EZH2 regulatory axis. *Cytotechnology.* 2024;76(2):231–246. doi: 10.1007/s10616-023-00612-z.
84. Zhu M, Yang L, Wang X. NEAT1 Knockdown suppresses the cisplatin resistance in ovarian cancer by regulating miR-770-5p/PARP1 axis. *Cancer Manag Res.* 2020;12:7277–7289. doi: 10.2147/cmar.s257311.
85. Wu YC, Ku MH, Huang WL, Dias L, Chen CW. NEAT1 in ovarian cancer: A key regulator of tumor progression, follicular fluid dynamics, and therapeutic resistance. *Anticancer Res.* 2025;45(3):825–842. doi: 10.21873/anticancer.17472.
86. Furuta E, Okuda H, Kobayashi A, Watabe K. Metabolic genes in cancer: Their roles in tumor progression and clinical implications. *Biochimica et Biophysica Acta - Rev Cancer.* 2010;1805(2):141–152. doi: 10.1016/j.bbcan.2010.01.005.
87. Jang M, Kim SS, Lee J. Cancer cell metabolism: implications for therapeutic targets. *Exp Mol Med.* 2013;45(10):e45–e45. doi: 10.1038/emmm.2013.85.
88. Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, et al. Cytochrome P450 enzymes and drug metabolism in humans. *Int J Mol Sci.* 2021;22(23):12808. doi: 10.3390/ijms222312808.
89. Kural C, Kaya Kocdogan A, Şimşek GG, Oğuztüzün S, Kaygın P, Yılmaz I, et al. Glutathione S-transferases and cytochrome P450 enzyme expression in patients with intracranial tumors: Preliminary report of 55 patients. *Med Principles Pract.* 2018;28(1):56–62. doi: 10.1159/000494496.
90. Mu W, Hu C, Zhang H, Qu Z, Cen J, Qiu Z, et al. miR-27b synergizes with anticancer drugs via p53 activation and CYP1B1 suppression. *Cell Res.* 2015;25(4):477–495. doi: 10.1038/cr.2015.23.
91. Pan YZ, Gao W, Yu AM. MicroRNAs regulate CYP3A4 expression via direct and indirect targeting. *Drug Metab Dispos.* 2009;37(10):2112–2117. doi: 10.1124/dmd.109.027680.
92. Kim I, Han N, Burckart GJ, Oh JM. Epigenetic changes in gene expression for drug-metabolizing enzymes and transporters. *Pharmacotherapy.* 2013;34(2):140–150. doi: 10.1002/phar.1362.
93. Klyushova LS, Perepechaeva ML, Grishanova AY. The role of CYP3A in health and disease. *Biomedicines.* 2022;10(11):2686. doi: 10.3390/biomedicines10112686.
94. Panda AC, Grammatikakis I, Munk R, Gorospe M, Abdelmohsen K. Emerging roles and context of circular RNAs. *WIREs RNA.* 2016;8(2). doi: 10.1002/wrna.1386.
95. Cai ZR, Hu Y, Liao K, Li H, Chen DL, Ju HQ. Circular RNAs: Emerging regulators of glucose metabolism in cancer. *Cancer Lett.* 2023;552:215978. doi: 10.1016/j.canlet.2022.215978.
96. Huang Y, He T, Zheng J, Chen J, Yang Z. Circular RNAs in metabolic health: bridging the gap between molecular biology and therapy. *Cell Death Dis.* 2026;17(1). doi: 10.1038/s41419-026-08450-5.
97. Collins JM, Wang D. Regulation of CYP3A4 and CYP3A5 by a lncRNA: a potential underlying mechanism explaining the association between CYP3A4*1G and CYP3A metabolism. *Pharmacogenet Genomics.* 2021;32(1):16–23. doi: 10.1097/fpc.0000000000000447.
98. Wu H, Liu B, Chen Z, Li G, Zhang Z. MSC-induced lncRNA HCP5 drove fatty acid oxidation through miR-3619-5p/AMPK/PGC1α/CEBPB axis to promote stemness and chemo-resistance of gastric cancer. *Cell Death Dis.* 2020;11(4). doi: 10.1038/s41419-020-2426-z.
99. Meng X, Bai X, Ke A, Li K, Lei Y, Ding S, et al. Long non-coding RNAs in drug resistance of gastric cancer: Complex mechanisms and potential clinical applications. *Biomolecules.* 2024;14(6):608. doi: 10.3390/biom14060608.
100. Havasi A, Cainap SS, Havasi AT, Cainap C. Ovarian cancer—insights into platinum resistance and overcoming it. *Medicina (B Aires).* 2023;59(3):544. doi: 10.3390/medicina59030544.
101. Al-Janabi I. The role of autophagy in the progression and treatment of tumors. *Al-Rafidain J Med Sci.* 2021;1:62–71. doi: 10.54133/ajms.v1i.37.
102. Klionsky DJ, Codogno P, Cuervo AM, Deretic V, Elazar Z, Fueyo-Margareto J, et al. A comprehensive glossary of autophagy-related molecules and processes. *Autophagy.* 2010;6(4):438–448. doi: 10.4161/auto.6.4.12244.
103. Chen W, Li Z, Liu H, Jiang S, Wang G, Sun L, et al. MicroRNA-30a targets BECLIN-1 to inactivate autophagy and sensitizes gastrointestinal stromal tumor cells to imatinib. *Cell Death Dis.* 2020;11(3). doi: 10.1038/s41419-020-2390-7.
104. Yang Y, Guo JX, Shao ZQ. miR-21 targets and inhibits tumor suppressor gene PTEN to promote prostate cancer cell proliferation and invasion: An experimental study. *Asian Pac J Trop Med.* 2017;10(1):87–91. doi: 10.1016/j.apjtm.2016.09.011.
105. Chen C, Demirkhanyan L, Gondi CS. The Multifaceted role of miR-21 in pancreatic cancers. *Cells.* 2024;13(11):948. doi: 10.3390/cells13110948.
106. Yao W, Guo P, Mu Q, Wang Y. Exosome-derived circ-PVT1 contributes to cisplatin resistance by regulating autophagy, invasion, and apoptosis via miR-30a-5p/YAP1 axis in gastric cancer cells. *Cancer Biother Radiopharm.* 2021;36(4):347–359. doi: 10.1089/cbr.2020.3578.
107. Fu Z, Luo W, Wang J, Peng T, Sun G, Shi J, et al. Malat1 activates autophagy and promotes cell proliferation by sponging miR-101 and upregulating STMN1, RAB5A and ATG4D expression in glioma. *Biochem Biophys Res Commun.* 2017;492(3):480–486. doi: 10.1016/j.bbrc.2017.08.070.
108. Nguyen LNT, Pyburn JS, Nguyen NL, Schank MB, Zhao J, Wang L, et al. Epigenetic regulation by lncRNA GAS5/miRNA/mRNA network in human diseases. *Int J Mol Sci.* 2025;26(3):1377. doi: 10.3390/ijms26031377.