Drug resistance is a major hurdle in cancer treatment and a key cause of poor prognosis. Epitranscriptomics and epiproteomics are crucial in cell proliferation, migration, invasion, and epithelial–mesenchymal transition. In recent years, epitranscriptomic and epiproteomic modification has been investigated on their roles in overcoming drug resistance. In this review article, we summarized the recent progress in overcoming cancer drug resistance in three novel aspects: (i) mRNA modification, which includes alternative splicing, A-to-I modification and mRNA methylation; (ii) noncoding RNAs modification, which involves miRNAs, IncRNAs, and circRNAs; and (iii) posttranslational modification on molecules encompasses drug inactivation/efflux, drug target modifications, DNA damage repair, cell death resistance, EMT, and metastasis. In addition, we discussed the therapeutic implications of targeting some classical chemotherapeutic drugs such as cisplatin, 5-fluorouridine, and gefitinib via these modifications. Taken together, this review highlights the importance of epitranscriptomic and epiproteomic modification in cancer drug resistance and provides new insights on potential therapeutic targets to reverse cancer drug resistance.

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INTRODUCTION

Drug resistance in cancer treatment

Cancer remains the leading cause of incidence and mortality worldwide.1,2 The development of cancer is a complex process with significant biological characteristics, such as abnormal cell proliferation and differentiation, a high degree of molecular heterogeneity and epithelial–mesenchymal transition (EMT).3 Because most cancers have progressed to the middle or late stages when diagnosed, molecular targeted drug therapy and chemotherapy are the main treatment options.4 The most common therapeutic drugs include cisplatin, sorafenib, oxaliplatin, 5-fluorouracil, and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs).5 However, long-term therapies usually lead to acquired drug resistance and poor prognosis. The main underlying mechanisms of drug resistance include: (1) drug efflux and alterations in drug metabolism; (2) alterations of drug targets; (3) DNA damage repair (DDR); (4) deregulation of apoptosis and autophagy; (5) resistance-promoting adaptive responses; (6) alterations in tumor microenvironment; and (7) epigenetic changes.6,7

Epigenetics refers to a “heritable” phenomenon in which the phenotype changes are independent of DNA sequence. Epitranscriptomics, also called “RNA epigenetics,”8 is a branch of epigenetics and refers RNA editing and noncoding RNA regulations. Epitranscriptomics plays essential roles in alternative splicing, nuclear export, transcript stability, and translation of RNAs.8 Epiproteomics is the posttranslational modifications (PTMs) that involve histone acetylation, SUMOylation, phosphorylation, and ubiquitination.9-12 The PTMs might regulate various biological processes via modulating chromosomal structures or regulating the binding of chromatin.13 Recent studies in RNA and protein modifications mainly focus on evaluating drug response to screening drugs suitable for individual patients or as the molecular targets to pioneer new ways of cancer treatment.14-17 In this review, we will discuss the role of posttranscriptional and PTM in cancer drug resistance and therapeutic targets.

mRNA modification in cancer drug resistance

In this section, we focus on the mechanism of cancer drug resistance in three different types of RNA modifications: alternative splicing, adenosine-to-inosine (A-to-I) modification, and mRNA methylation (Fig. 1 and Table 1).

Alternative splicing and cancer drug resistance. Alternative splicing is a process by which introns are differentially removed from a single precursor mRNA (pre-mRNA) to generate multiple mature mRNA products.16,19 More than 95% of human genes are transcribed into pre-mRNAs that undergo alternative splicing.20-22 Since alternative splicing represents a frequent mechanism underlying the expansion of transcriptomes and proteomes in higher eukaryotes, it plays numerous critical roles in both normal and disease processes. Global analysis has revealed at least 15,000 cancer-specific splice variants in 27 types of cancers,20 indicating that alternative splicing is a significant mechanism contributing to the development of cancer.
Fig. 1 mRNA modification in cancer drug resistance. a Schematic representation of examples of alternative splicing patterns causing cancer drug resistance, including skipping of one exon, skipping of multiple exons, mutually exclusive exons, and exon inclusion. b Schematic representation of A-to-I RNA editing mediated drug-resistance-related functional consequences including structure modification of targeted protein, target escape from silencing of miRNA, off-target effects of miRNA, pre-miRNA degradation, aberrant splicing of targeted mRNA. c Schematic representation of m^6^A modification network in targeted genes causing cancer drug resistance. In the nucleus, m^6^A is deposited in nascent pre-mRNA by a “writer” multiprotein complex (i.e., METTL3, METTL14, and other related protein) and removed by “eraser” demethylases (i.e., FTO and ALKBH5). In the cytoplasm, the m^6^A modifications are recognized by “reader” proteins, resulting in stabilization or decay or enhanced translation. Specific examples of each mRNA modification event discussed in the text are shown.
| Cancer type                                      | Target gene | RNA modification | Drug/ molecule | Molecular mechanisms                                                                 | Reference |
|-------------------------------------------------|-------------|------------------|----------------|---------------------------------------------------------------------------------------|-----------|
| Skipping of one exon during splicing            | Leukemia    | FPGS             | Aberrant splicing | Methotrexate                                                                           | 23        |
|                                                 | B-ALL       | CD19             | Aberrant splicing | CART-19                                                                               | 24        |
|                                                 | Breast cancer, ovary cancer cells | BRCA1 | Aberrant splicing | Cisplatin PARP inhibitors                                                               | 26        |
| Skipping of multiple exons during splicing      | Melanoma    | BRAF V600E       | Aberrant splicing | Vemurafenib BRAF inhibitor                                                             | 27,28     |
|                                                 | Prostate cancer | AR-V7 | Aberrant splicing | Enzalutamide Abiraterone                                                              | 29        |
| Mutually exclusive exons by aberrant splicing   | CML NSCLC   | BIM              | Aberrant splicing | TKIs                                                                                  | 30        |
| Intron retention by aberrant splicing           | Burkitt lymphoma | STAT2 | Aberrant splicing | IFN, camptothecin, staurosporine, doxorubicin                                         | 31        |
| A-to-I editing in coding gene                   | Myeloma     | GLI1             | A-to-I editing   | Immunotherapy                                                                          | 38        |
| A-to-I editing in miRNA                         | Leukemia    | miR-let-7        | A-to-I editing   | ADAR1-mediated A-to-I editing impairs let-7 biogenesis leading to LSC self-renewal     | 42        |
|                                                 | Breast cancer | miR-25-3p | A-to-I editing | Methotrexate                                                                           | 43        |
| A-to-I editing in 3' UTR                        | CML         | MDM2             | A-to-I editing   | Chemotherapy                                                                           | 44        |
| A-to-I editing in intron                        | Leukemia    | GSK3β            | A-to-I editing   | TKIs                                                                                  | 45        |
| m^6A Writer regulation                         | Glioma      | SOX2             | m^6A methylation | Radiotherapy                                                                           | 63        |
|                                                 | Lung cancer  | EGFR             | m^6A methylation | TKIs                                                                                  | 64        |
| m^6A Reader regulation                         | AML         | TNFRSF2          | m^6A methylation | TNF-induced apoptosis                                                                  | 65        |
| Target gene | RNA modification | Drug/ molecule | Molecular mechanisms | Reference |
|-------------|------------------|----------------|----------------------|-----------|
| FZD10       | m6A methylation  | METTL3         | m6A Eraser regulation | 66        |
|             | m6A methylation  |                | yRNA downregulator     | 66        |
|             | m6A methylation  |                | YTHDF1/3 and eIF3b      | 68        |
|             | m6A methylation  |                | METTL3                  | 68        |
|             | m6A methylation  |                | YAP                     | 68        |
|             | PD-1 antibody    |                |                       | 68        |
|             | m6A methylation  |                |                       | 68        |
|             | m6A methylation  |                |                       | 68        |
|             | m6A methylation  |                |                       | 68        |

**Table 1.** Continued

Epitranscriptomics and epiproteomics in cancer drug resistance.

| Reference | Description |
|-----------|-------------|
| 66        | METTL3, which is the key enzyme of m6A modification, leading to overcame PARP inhibitor resistance |
| 68        | Overexpression of FTO decreases m6A methylation in PD-1 mRNA, leading to PD-1 mRNA decay through YTHDF2 regulation |

**Exon skipping is one of the most important alternative splicing processes in drug-resistant cancer cells.** In leukemia, the enzyme folylpolyglutamate synthetase (FPGS) is responsible for the intracellular retention of folates and antifolates by polyglutamylation. Abrupt splicing of FPGS induced skipping of exon 12 and generated a nonfunctional FPGS enzyme, which leads to reduced retention of antifolates and causes cancer cells resistant to folate antagonist methotrexate. In patients with B-cell malignancies treated with adoptive T cells expressed chimeric antigen receptors against CD19 (CART-19), the expression of alternatively spliced CD19 isoform lacking exon 2 caused failure of initiation of CART-19-mediated cancer cell death. TGF-β-activated kinase 1 (TAK1) promoted TGF-β-induced apoptosis in response to TGF-β activation. However, TAK1 variable exon 12 exerted opposite function that constitutively supported TGF-β-induced EMT and activated nuclear factor-kappa B (NF-kB) signaling pathway, eventually causing chemotherapeutic resistance. Breast and ovary cancer cells can overcome deleterious germline mutations in BRCA1 (the gene encoding breast cancer type-1 susceptibility protein) by alternative splicing. Among the splicing products, BRCA1-Δ11q retains residual activity, triggering resistance to cisplatin and poly ADP-ribose polymerase (PARP) inhibitors.

In order to escape from drug mediated apoptosis, targeted genes would undergo multiple exons skipping to delete the specific domains targeted by cancer drugs. BRAF is an oncogene belonging to RAS/MAPK signaling pathway, which controls several important cellular functions including proliferation and migration. About 90% of melanomas harbor BRAF V600E mutation, which leads to the constitutive activation of RAS/MAPK signaling pathway and malignant cell proliferation. Vemurafenib is a potent RAF kinase inhibitor with remarkable clinical activity against BRAF (V600E) melanoma. However, patients rapidly develop resistance to vemurafenib treatment. Mechanistically, patients harboring isoform BRAF3-9 (Δ exons 4-8) or BRAF2-6 (Δ exons 3-5) that could eliminate RAS-binding domains often develop drug resistance. Advanced prostate cancer is commonly treated with drugs that inhibit androgen biosynthesis or antagonize the interaction between androgen and androgen receptor (AR). AR splice variant 7, which lacked the ligand-binding domain (exon 4–8), was constitutively resistant to androgen-targeted therapies. Mutually exclusive exons represent a rare subtype of RNA splicing. However, once it occurs, the cells harboring the spliced product with drug-resistant function would be evolutionally selected and accumulated resulting in cancer drug resistance. B-cell CLL/lymphoma 2 (BCL-2)-like 11 (BIM), a pro-apoptotic member of the BCL-2 family, is required for TKIs to induce apoptosis in kinase-driven cancers. A polymorphism switched BIM splicing from exon 3 to exon 4 would result in deletion of pro-apoptotic BCL-2-homology domain 3 (B3H) and confer intrinsic TKI resistance in both CML and EGFR NSCLC cells. Patients with this mutant protein had a poorer response to tyrosine kinase inhibitors than individuals without the polymorphism. In addition to exon removal and switching, intron retention is another mechanism that cancer cells applied for drug resistance. Interferon (IFN) treatment is effective in hematological malignancies through mediating cell apoptosis. Signal transducer and activator of transcription 2 (STAT2) is a transcription factor that contributes to the activation of IFN responsive genes. However, cancer cells
protein “readers”, and the m^t^A mark can be removed by demethylase “erasers”. The core m^A writer complex includes methyltransferase-like 3 (METTL3) and methyltransferase-like 14 (METTL14). The m^A erasers include fat mass and obesity-associated (FTO) and ALKB homolog 5 (ALKBHS) demethylases.

The readers were firstly discovered to be YTHF2-B homology (YTH) domain-containing proteins (YTHDF1, 2, 3 and YTHDC1, 2). Soon afterward, more different types of readers were revealed. Interestingly, they exert diverse functions with different mechanisms. For example, YTHDF2 specifically recognizes and destabilizes m^A modified RNAs and re-localizes these RNAs to processing bodies; while YTHDF1 stimulates mRNA translation by interacting with translation initiation factors. The m^A marks are enriched at the RAR target (R = G or A, H = A; C, or U) motif around stop codons, 3′ or 5′ UTRs, and internal long exons. The m^A deposition is the beginning of the journey of methylation regulation. The mRNA might be demethylated by erasers, or exported into cytoplasm and subject to be “read”. The dramatic and dynamic variations of mRNA modifications had been found in every step of biological processing, especially in tumor transformation and cellular reprogramming, implying their biological significance in cancer therapeutic treatment.

The biological significance of mRNA methylation is recently uncovered, however, the mechanism of regulation of m^A modification in drug resistance remains poorly understood. Most studies focused on the regulation of the transcripts that participated in the maintenance and modulation of the stemness and self-renewing CSCs that are thought to be responsible for complex tumor heterogeneity, cancer progression and therapeutic resistance.59–61 SOX2 is one of the major regulators in tumor initiation and cancer stem-cell functions.62 One Study showed that m^A writer METTL3 interacted with the 3′ UTR of Sox2 mRNA and lead to methylation and stabilization of Sox2 mRNA in glioma stem-like cells (GSCs). The enhanced expression of METTL3 increased Sox2 expression, which maintained the stemness and radiosensitivity of GSCs. Interestingly, METTL3 is a multifunctional protein that not only has the activity of transmethylation, but can also regulate the mRNA translation in cytoplasm. In lung cancer, METTL3 promoted translation of oncogenic mRNA, epidermal growth factor receptor (EGFR), independent of its catalytic activity. METTL3 shuttled from nucleus to cytoplasm and interacted with ribosomes. Such interactions promoted EGFR mRNA translation leading to cell proliferation, survival, and induction of expansion of cancers.

The process of “reading” and “erasing” of m^A methylation marks are essential for regulation of genes that are responsible for drug resistance. In acute myeloid leukemia (AML), YTHDF2 is overexpressed and is required for disease initiation. Deletion of reader YTHDF2 compromises LSC development and propagation by increasing the half-life of tumor necrosis factor receptor 2 (TNFR2). Importantly, YTHDF2 is not essential for normal hematopoietic stem cells, indicating that YTHDF2 is a unique therapeutic target which specifically inhibits LSCs. In cervical cancer, FTO was found to induce DNA repair activity and drug resistance to chemoradiotherapy by increasing β-catenin mRNA through m^A methylation.64,65 Recently, inhibition of m^A eraser was found to be a potential strategy for overcoming drug resistance. Inhibition of m^A demethylases FTO and ALKBHS was found to effectively overcome PARP inhibitor resistance in BRCA-mutated epithelial ovarian cancers. Mechanistically, deletion of m^A erasers increased Fzd10 mRNA m^A modification and led to stabilization of Fzd10 and upregulation of the Wnt/beta-catenin signaling pathway.

In some cases, METTL3 promotes drug resistance through various pathways simultaneously. For example, METTL3 increased the mRNA of YAP, an effector of Hippo signaling pathway, leading to promotion of castration resistance in direct and indirect
mRNA.69 chemoresistance.70 gefitinib-resistant cells.71 LncRNA can directly interact with target genes, or act as ceRNA to interact with miRNA to participate in gene expressions; circRNAs can act as “miRNA sponge” to release the inhibitory effect of miRNA on its target genes. The noncoding RNAs could be potential targets of drug resistance in cancers due to their functions in cell proliferation, metastasis, and EMT.

mRNAs and cancer drug resistance. Recent studies have shown that miRNAs are involved in cisplatin (DDP)-mediated cancer drug resistance. Ubiquitin-conjugating enzyme E2C (UBE2C) is an active proto-oncogene and highly expressed in DDP-resistant NSCLC cells. miR-495 targeted 3'UTR of UBE2C, which acted as a transcriptional factor and downregulated the expression of cancer drug resistance associated genes such as ABCG2 and ERCC1, thus reversing DDP resistance in NSCLC cells via reducing EMT, cell migration, and invasion.81 Another miRNA, miR-146b could bind to protein tyrosine phosphatase 1B, inhibit the EMT process, and reduce cisplatin resistance in human lung adenocarcinoma (LUAD) cells.82 Analysis of miRNA expression profiles and experiments in cisplatin-resistant and -sensitive ovarian cancer cells showed that miR-141 was overexpressed in cisplatin-resistant cells. miR-141 could directly target KEAP1, an oxidative stress regulator, and induced cisplatin resistance in ovarian cancer cells by activating NF-κB pathway.83 Exosomes are vesicles with a diameter of 40–100 nm. They play important roles in regulating tumor microenvironment, metastasis, and drug resistance by promoting transportation of miRNAs and mRNAs.84,85 The cancer-associated fibroblasts derived exosomal miR-196a accelerated head and neck cancer cell proliferation and cisplatin resistance through down-regulating expression of target genes: CDKN1B and INGS.86 miR-936 suppressed cell proliferation, migration in glioma and, non-small cell lung cancer,86 and induced drug resistance to cisplatin and DOX via targeting G protein-coupled receptor 78 (GRP78) in laryngeal squamous cell carcinoma cells.87

In addition, other EGFR-TKIs involved in drug resistance through regulating miRNAs expressions. Notch receptor 3 (NOTCH3) is highly expressed in LUAD and gefitinib-resistant cells. MR-150 decreased IC50 of gefitinib, downregulated the expressions of target gene NOTCH3, which was positively correlated with collagen 1A1 expression, providing a potential therapeutic target for LUAD treatment.89 Bone morphogenetic protein 4 (BMP4) accelerates cancer cell energy metabolism and is upregulated in the EGFR-TK1-resistant cells. However, low-expression of miR-139-5p was found in TKI-resistant cells and combination of miR-139-5p and yuanhuadine significantly suppressed BMP4 expression and tumor growth in the resistant NSCLC cells and cell-derived xenograft (CDX) mouse model.90 Microarray analysis revealed that miR-214-3p was significantly decreased in multidrug resistant cells. MiR-214-3p directly targeted ABCB1 and XIAP, promoted cell apoptosis, and sensitized retinoblastoma cells to multiple chemotherapeutic drugs. Overexpression of ABCB1 or XIAP could reverse chemoresistance induced by miR-214-3p.92 Tao et al. showed that miR-451a promoted the sensitivity of lung cancer cells to DOX via targeting c-myc to reduce expression of N-cadherin and Vimentin and enhance expression of E-cadherin.93 Han et al. revealed that miR-552 could promote the self-renewal, tumorigenesis. and sorafenib resistance via activating protein kinase B (Akt) phosphorylation in liver tumor-initiating cells (T-ICs).94

Fig. 2 The functions of noncoding RNAs in cancer drug resistance. LncRNA can directly interact with target genes, or act as ceRNA to interact with miRNA to participate in gene expressions; circRNAs can act as “miRNA sponge” to release the inhibitory effect of miRNA on its target genes. The noncoding RNAs could be potential targets of drug resistance in cancers due to their functions in cell proliferation, metastasis, and EMT.
circAKT3 upregulated PIK3R1 expression via sponging miR-198 and promoted cisplatin resistance in gastric cancer.114 CircPAN3 induced DOX resistance in acute myeloid leukemia via regulating autophagy-associated AMPK/mTOR signaling pathway and protein expressions of LC3II/I and p62.115 or miR-153-5p/miR-183-5p-XIAP axis.116 Hsa_circ_0079662 interacted with hsa-miR-324-5p as the ceRNA and enhanced the resistance to oxaliplatin via TNF-α pathway in human colon cancer.117 Hsa_circ_0060060 accelerated expressions of autophagy marker LC3 and p62 through miR-144-3p/TGF-α axis and promoted cisplatin resistance in papillary thyroid carcinoma and anaplastic thyroid carcinoma cells.118 In addition, circCELSR1 was upregulated in paclitaxel-resistant ovarian cancer cells. Inhibition of circCELSR1 enhanced paclitaxel-induced cytotoxicity via upregulating FOXR2 expression or acting as the sponge for miR-1252 and increased cell apoptosis.119 Dong et al found that circ_0076305 was upregulated in NSCLC and promoted cisplatin resistance in NSCLC by upregulating STAT3 via targeting miR-295-5p.120

However, some studies indicated that circRNAs increased cancer drug sensitivity. For example, Li et al. showed that circ_0002483 enhanced paclitaxel sensitivity in NSCLC by targeting GRB2, FOXO1, and FOXO3 via miR-182-5p.121 Sang et al. found that Hsa_circ_0025202 could inhibit tumor progression and enhance the sensitivity of cancer cells to tamoxifen in breast cancer via targeting miR-182-5p/FOXO3a axis.122 Moreover, Liang et al. indicated that decreased expression of circDMAC4 in breast cancer suppressed DOX resistance through miR-548p/PBLD pathway.123 The roles and the molecular mechanisms of noncoding RNAs in cancer drug resistance are outlined in Table 2.

Protein modification in cancer drug resistance
PTM refers to the enzymatic modification after the biosynthesis of proteins, which is crucial for regulating and maintaining the functions of proteins. A large portion of human proteins have gone through at least one round of PTM after being synthesized. The PTM status of human proteins retrieved from Uniprot database (www.uniprot.org) is summarized and illustrated in Fig. 4. Among different types of PTMs, phosphorylation is the most common one, with 7977 human proteins containing 40,694 phosphorylation sites, and serine is the most common phosphorylated amino acid. Among these 7977 proteins, the top-five enriched GO biological processes are “organelle organization,” “cell localization,” “regulation of cellular component organization,” “positive regulation of metabolic process,” and “establishment of localization in cell.” Acetylation ranks the second, with 3379 human proteins containing 6604 acetylation sites, and lysine is the most preferred acetylation amino acid. Among these 3379 proteins, the top-five enriched GO biological processes are “organelle organization,” “cellular catabolic process,” “mRNA metabolic process,” “catabolic process,” and “organic substance catabolic process.” Ubiquitination ranks the third, with 1025 proteins being ubiquitinated. Among these 1025 proteins, the top-five enriched GO biological processes are “organelle organization,” “catabolic process,” “mRNA metabolic process,” “catabolic process,” and “organic substance catabolic process.” Glycosylation ranks the fifth, with 811 proteins containing 4534 glycosylation sites, and asparagine is the most preferred glycosylation amino acid. Among these 811 proteins, the top-five enriched GO biological processes are “mRNA metabolic process,” “organelle organization,” “small GTPase-mediated signal transduction,” “mRNA processing,” and “Ras protein signal transduction.” Methylation ranks the fourth, with 1216 methylation sites, and asparagine is the most ordinary methylation amino acid. Among these 1216 proteins, the top-five enriched GO biological processes are “mRNA metabolic process,” “positive regulation of metabolic process,” “protein modification process,” “macromolecule modification,” “protein modification by small protein conjugation or removal,” and “positive regulation of metabolic process.”

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Table 2. Noncoding RNAs in cancer drug resistance

| Noncoding RNA               | Target gene                  | Cancer                                | Function      | Drug         | Reference |
|-----------------------------|------------------------------|---------------------------------------|---------------|--------------|-----------|
| miR-495                     | ABCG2, ERCC1                 | Lung cancer cells                     | Drug sensitivity | Cisplatin   | 81        |
| miR-146b                    | PTP1B                        | Lung cancer cells                     | Drug sensitivity | Cisplatin   | 82        |
| miR-141                     | KEAP1                        | Ovarian cancer                        | Drug resistance | Cisplatin   | 83        |
| miR-196a                    | CDKN1B, ING5                 | Head and neck cancer                  | Drug resistance | Cisplatin   | 86        |
| miR-936                     | GPR78                        | Laryngeal squamous cell carcinoma     | Drug resistance | Cisplatin   | 89        |
| miR-150                     | NOTCH3                       | Lung adenocarcinoma                   | Drug sensitivity | Gefitinib  | 90        |
| miR-214-3p                  | ABCB1, XIAP                  | Retinoblastoma cells                  | Drug sensitivity | Multiple chemodrugs | 92 |
| miR-451a                    | N-cadherin, Vimentin and E-cadherin | Lung cancer cells              | Drug sensitivity | Doxorubicin | 93        |
| miR-552                     | PTEN                         | Liver tumor-initiating cells          | Drug resistance | Sorafenib   | 94        |
| LncRNA MIR100HG             | GATA6                        | Colorectal and head and neck squamous cell cancer | Drug resistance | Cetuximab   | 96        |
| LncRNA MALAT1               | ZFP91, ATG5, ATG12, HIF-2α   | Gastric cancer and hepatocellular carcinoma cancer | Drug resistance | Oxaliplatin, Cisplatin | 98 |
| LncRNA KCNQ1OT1             | TSPAN3                       | Acute myeloid leukemia                | Drug resistance | Adriamycin  | 100       |
| LncRNA-HOTAIR               | ULK1                         | Lung cancer                           | Drug resistance | Crizotinib   | 105       |
| LncRNA LINCO0160            | PIK3R3                       | Hepatocellular carcinoma cancer       | Drug resistance | Sorafenib   | 106       |
| LncRNA SNHG6                | ULK1                         | Colorectal cancer                     | Drug resistance | 5-fluorouracil | 110 |
| LncRNA SNHG14               | RAB5A and ATG4D              | Pancreatic cancer                     | Drug resistance | Gemcitabine | 112       |
| CircAKT3                    | PIK3R1                       | Gastric cancer                        | Drug resistance | Cisplatin   | 114       |
| CircPAN3                    | LC3I/II, p62 and XIAP        | Acute myeloid leukemia                | Drug resistance | Doxorubicin | 115, 116  |
| Hsa_circ_0079662            | HOXA9                        | Colon cancer                          | Drug resistance | Oxaliplatin | 117       |
| Hsa_circ_0060060            | TGF-α                        | Papillary thyroid carcinoma and Anaplastic thyroid carcinoma cancer | Drug resistance | Cisplatin   | 118       |
| CircELSR1                   | FOXR2                        | Ovarian cancer                        | Drug resistance | Paclitaxel  | 119       |
| Circ_0076305                | STAT3                        | Lung cancer                           | Drug resistance | Cisplatin   | 120       |
| Circ_002483                 | GRB2, FOXO1, and FOXO3       | Lung cancer                           | Drug sensitivity | Taxol       | 121       |
| Hsa_circ_0025202            | FOXO3a                       | Breast cancer                         | Drug sensitivity | Tamoxifen   | 122       |
| CircKDM4C                   | PBLD                         | Breast cancer                         | Drug sensitivity | Doxorubicin | 123       |

*ABCG2 ATP-binding cassette subfamily G member 2, ERCC1 ERCC excision repair 1, endonuclease non-catalytic subunit, PTP1B protein tyrosine phosphatase non-receptor type 1, KEAP1 kelch like ECH associated protein 1, CDKN1B cyclin dependent kinase inhibitor 1B, INGS inhibitor of growth family member 5, GPR78 G protein-coupled receptor 78, NOTCH3 notch receptor 3, ABCB1 ATP-binding cassette subfamily B member 1, XIAP X-linked inhibitor of apoptosis, PTDN phosphatase and tensin homolog, GATA6 GATA binding protein 6, MGST1 microsomal glutathione S-transferase 1, MGST3 microsomal glutathione S-transferase 3, ZFP91 ZFP91 zinc finger protein, ATG5 autophagy-related 5, ATG12 autophagy related 12, TSPAN3 tetratraspanin 3, ULK1 unc-51 like autophagy activating kinase 1, PIK3R3 phosphoinositide-3-kinase regulatory subunit 3, ATG4D autophagy related 4D cysteine peptidase, PIK3R1 phosphoinositide-3-kinase regulatory subunit 1, XIAP X-linked inhibitor of apoptosis, HOXA9 homeobox A9, TGF-α transforming growth factor alpha, FOXR2 forkhead box R2, STAT3 signal transducer and activator of transcription 3, GRB2 growth factor receptor bound protein 2, FOXO1 forkhead box O1, FOXO3 forkhead box O3, PBLD phenazine biosynthesis like protein domain containing*
mechanisms of PTMs in chemoresistance can either be direct, in which the modifications disrupt binding sites; or indirect, in which upstream modifications lead to pathway blockage. In this section, we will briefly discuss the role of PTM in chemoresistance from the perspectives of drug inactivation/efflux, drug target modifications, DDR, cell death resistance, EMT and metastasis. Some of the reported protein targets causing chemoresistance are listed in Table 3.

**Drug inactivation.** Certain drugs need metabolic modification to become their active forms, and some cancer cells have developed the ability to modify/shut down these activation processes or to use other processes to deactivate the active forms of drugs. For example, capecitabine, under the brand name Xeloda, is a widely used chemotherapeutic drug in the treatment of breast cancer, gastric cancer, and colorectal cancer. In terms of 5-FU, although there have been activation and deactivation processes in many cancer types, drug efflux also contributes to the chemoresistance (Fig. 5b). 5-FU and its downstream product fluorodeoxyuridylate (FdUMP) can be converted to its active form, 5-FU, which is effective in cancer treatments; on the other side, TYMP has been found as a pro- oncogenic in many studies, where it is overexpressed in many types of cancers, and the overexpression of TYMP promotes tumor angiogenesis and inhibits apoptosis. As for CES and CDA, although there haven't been any direct evidence, the changes of catalytic activity of CES and CDA genes in some cancer patients with SNPs might be related to PTMs. Aside from mutations, CES is also positively regulated by p53, a well-known tumor suppressor, which is often mutated or posttranslational modified in cancer cells (will be discussed in the following context). Hence the downregulation of CES expression in cancers can result in chemoresistance.

Aside from impeding the activation process, deactivation also contributes to drug resistance. For example, dihydropyrimidine dehydrogenase (DPD) is a key enzyme in pyrimidine catabolism, and is capable of reducing the pyrimidine double bonds of 5-FU, and converting it to dihydouracil. This process deactivates 5-FU and also results in chemoresistance. In certain type of cancer (e.g., head and neck squamous cell carcinoma), DPD is overexpressed, and overexpression of DPD is one of the main reasons causing 5-FU resistance.

**Drug efflux.** Efflux is the process of moving a variety of compounds out of cells, which is mediated by some ATP-binding cassette (ABC) transporters, which are also named multiple drug resistance (MDR) proteins. Among them, P-glycoprotein, encoded by ABCB1 (MDR1), is one of the most widely studied transporters. P-glycoprotein is highly expressed in many drug-resistant tumors and is involved in the efflux of many anticancer drugs such as anthracycline, daunorubicin, epipodophyllotoxins, and others (Fig. 5b). The regulation of P-glycoprotein is explored in many studies: Takada et al. showed that the expression of P-glycoprotein was positively regulated by MAPFK signaling pathways in human breast cancer; Henrique et al. found that ABCB1 was epigenetically regulated through posttranslational histone modification in prostate cancer; Xie et al. revealed that Pim-1 could phosphorylate P-glycoprotein, which protects P-glycoprotein from degradation and enables its glycosylation. Overexpression of Pim-1 in many human cancers indirectly contributes to P-glycoprotein-mediated drug-efflux and chemoresistance. The Pim-1 inhibitor SGI-1776 was reported to overcome P-gp-mediated drug resistance.

In terms of 5-FU, although there have been activation and deactivation processes in many cancer types, drug efflux also contributes to the chemoresistance (Fig. 5b). 5-FU and its downstream product fluorodeoxyuridylate (FdUMP) can be

**Fig. 4**  The PTM status of human proteins. All data is retrieved from Uniprot database and updated as of 2015-05. The number of proteins with different types of PTMs are illustrated in the barplot (left); the percentages of amino acids modified in each type of PTMs are illustrated in the circle plots (right).
pumped out of cells through several transporters such as ABCC3/4/5/11. PTMs play important roles in these ABC transporter-mediated drug resistance, e.g., phosphorylation directly affects the efficiency of transporters; glycosylation influences the stability of transporters and protects them from proteases.

Drug target modification. Most of the cancer drugs aim for some specific proteins, causing structural changes of targets, leading to the blockage of certain pathways, and resulting in death of cancer cells. To resist these effects, many cancer cells alter the target proteins either by decreasing/halting their expression or modifying their structures to hinder the binding process (Fig. 5c). For example, EGFR, one of the most intensively studied receptor-tyrosine kinases (RTKs), was found to have a variety of mutations and PTMs that resulted in multiple chemoresistance in many different types of cancers: T790M mutation was directly related to gefitinib and erlotinib resistance in non-small cell lung cancer; lack of glycan sialylation due to K521 polymorphism resulted in cetuximab resistance in head and neck cancers; methylation of R1175 by PRMT5 modulated EGF-induced phosphorylation at W1173, which further promotes ERK activation in breast cancer; SRC kinase-mediated EGFR ubiquitination, and degradation in colorectal cancer. Aside from EGFR, other ErbB family members also showed alterations in many cancers. Phosphorylation by PKB inhibited the activation of HER2 in breast cancer and resulted in resistance to herceptin; neural precursor cell expressed and developmentally downregulated 4, an E3 ubiquitin ligase, mediated the degradation of HER3 in prostate cancer through ubiquitination.

Cancer cells could also use alternative pathways to bypass or compensate for drug actions. For example, VanMeter et al. revealed an alternative mechanism of downstream protein activation, which is independent of EGFR in non-small cell lung cancer; Sergina et al. showed that overexpression of MCL-1/BCL-2 and repression of BAX/BAK proteins also contribute to this process. The repression of autophagy in cancer cells. MTORC1 is triggered through PI3K-AKT pathways, which further inhibits the phosphorylation of ULK1, and impedes the autophagy process. The activation of EMT in cancer cells. EMT process is triggered through multiple signaling pathways including TGFβR and WntR, which activate SNAIL and TWIST transcription factors. These EMT-TFs repress the expression of E-cadherin and promote the expression of N-cadherin, vimentin, and fibronectin, which further promote EMT process.
apoptosis and results in cell death (Fig. 5d). Increasing DNA repair and damage tolerance as well as evading apoptosis were the potential mechanisms of chemotherapeutic resistance in cancer cells. After chemotherapeutic treatment, DDR could induce a rapid but faulty repair mechanism, and the tolerance of DNA damages were achieved through several specialized DNA polymerases, such as poly beta, kappa, and zeta, that had low fidelity in DNA duplication and resulted in mutations. The overexpression of these specialized polymerases in chemoresistant cancers has been revealed in many studies. For example, elevated expression of Poly beta had been found in drug-resistant cancer cells, and knockdown of Poly beta by siRNA resensitized cancer cells to cisplatin; upregulated poly kappa had also been examined in lung cancer and inactivation of p53 promoted the expression of poly kappa. The genomic instability caused by tolerance of mutations was one of the main features of cancer.

Ataxia-telangiectasia-mutated (ATM) and ataxia-telangiectasia and Rad3-related (ATR) kinases are activated by stresses of DNA double strand breaks and single strand breaks. Activation of ATM/ATR induces cell-cycle arrest (through CHK1 and CHK2) and cell apoptosis (through p53). In many cancer cells, the expression of ATM/ATR is downregulated and the activity of ATM/ATR is also reduced by upregulating WIP1 phosphatase, which dephosphorylates ATM/ATR and its substrates, e.g., p53. Interestingly, in certain types of cancers, where ATM/ATR is uncoupled from cell-cycle arrest and apoptosis, the overexpression of ATM/ATR has been found in many studies, which proves the importance of ATM/ATR in chemoresistance.

Cell death resistance. A significant hallmark of cancer cells is the ability of resisting cell death; hence evading apoptosis and autophagy is one of the most important abilities of cancer cells. In normal cells, apoptosis is induced either through extrinsic or intrinsic signaling pathways. In cancer cells, the components in both extrinsic and intrinsic signaling pathways are either mutated or mis-regulated, therefore apoptosis process is impeded (Fig. 5e). For example, extrinsic apoptosis pathways were triggered by surface death receptors such as FAS, DR4/5, and in many cancers those death receptors were often mutated or PTM modified, that greatly impeded apoptosis process. Moreover, some decoy receptors such as TRID and TRUND were overexpressed in certain cancers, which repressed extrinsic signaling pathway-induced apoptosis. Intrinsic signaling pathways are mainly induced by p53, which is often mutated or modified in cancer cells, as reviewed in Manoson et al. resulted in inhibiting the intrinsic apoptosis process from very beginning. Aside from p53 mutation, p65 subunit of nuclear factor-kappa B, is one of the regulators of tumorigenesis, and the suppression of p65 signaling could enhance the DOX-induced apoptosis in cervical cancer. MCL-1/BCL-2, the anti-apoptotic proteins, was found to be overexpressed in many types of cancers. BAX, the pro-apoptotic protein, could be phosphorylated by AKT at residue 184 in breast cancer, which prevented it from entering into mitochondria, resulting in chemoresistance. Caspase 3, the executioner of apoptosis, was phosphorylated by p38-MAPK, which was negatively regulated by TYMP, and the overexpression of TYMP in many cancers helped cancer cell to evade apoptosis and contributed to chemoresistance. showed that EL4 cells overexpressing Bcl-XL or DNc3 (a dominant negative form of caspase 3) proteins exhibited multidrug resistance such as DOX, and these EL4 cells could be eliminated by antigen-specific primed cytotoxic T cells. Recently, Hu et al. have showed that culling-ring ubiquitin ligase 4 (CRL4) could regulate the expression of BIRC3 (one of the inhibitors of apoptosis proteins) through STAT3 pathway, and BIRC3 is associated with cisplatin-resistance in ovarian cancer cells, suggesting the potential functional role of CRL4 and BIRC3 as novel therapeutic targets for cisplatin-resistant patients.

Epitranscriptomics and epiproteomics in cancer drug resistance:... Song et al.
Epitranscriptomics and epiproteomics in cancer drug resistance: Epigenetic alterations in epitranscriptomic and epiproteomic modifications play critical roles in cancer treatment and drug resistance. Future researches on the function of epigenetics in vivo and its effect on conquering drug resistance are warranted. For example, though emerging evidences have indicated that m6A regulators play important roles in cancer drug resistance by modulating the epitranscriptome, the research on m6A methyltransferase family is mainly focused on METTL3 and METTL14, and the underlying molecular mechanisms of other m6A methyltransferase members in drug resistance need to be further investigation. Recently, miRNAs have been discovered in exosomes, a structure that contained abundant genetic information and widely distributed in various body fluids. The potential advantages of miRNAs in exosomes imply that the roles in cancer drug resistance are worthy explored. The mutations related to cancer drug resistance have been identified, such as EGFR T790M and C797S. However, the relationship between mutations and protein expressions is not fully consistent. Temporal proteomic is being used as an emerging technology to target drug resistance and researchers showed that the combination of KRASi and HSP90 inhibitor (17-AAG) or cell-cycle inhibitor (CDK4/6i) could block cell growth and inhibit cancer drug resistance, which suggested that proteomic can be used as an effective treatment strategy for overcoming cancer drug resistance. Overall, targeting epigenetic alterations may improve cancer treatment and provide new approaches in overcoming drug resistance.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Epigenetic alternations in epitranscriptomic and epiproteomic modifications play critical roles in cancer treatment and drug resistance. Future researches on the function of epigenetics in vivo and its effect on conquering drug resistance are warranted. For example, even though emerging evidences have indicated that m6A regulators play important roles in cancer drug resistance by modulating the epitranscriptome, the research on m6A methyltransferase family is mainly focused on METTL3 and METTL14, and the underlying molecular mechanisms of other m6A methyltransferase members in drug resistance need to be further investigation. Recently, miRNAs have been discovered in exosomes, a structure that contained abundant genetic information and widely distributed in various body fluids. The potential advantages of miRNAs in exosomes imply that the roles in cancer drug resistance are worthy explored. The mutations related to cancer drug resistance have been identified, such as EGFR T790M and C797S. However, the relationship between mutations and protein expressions is not fully consistent. Temporal proteomic is being used as an emerging technology to target drug resistance and researchers showed that the combination of KRASi and HSP90 inhibitor (17-AAG) or cell-cycle inhibitor (CDK4/6i) could block cell growth and inhibit cancer drug resistance, which suggested that proteomic can be used as an effective treatment strategy for overcoming cancer drug resistance. Overall, targeting epigenetic alterations may improve cancer treatment and provide new approaches in overcoming drug resistance.

Epiproteomic modifications Various studies have indicated that targeting epiproteomic modifications can ameliorate drug resistance in cancers (Fig. 6). Histone methyltransferase SMYD2 promoted tumor progression in renal cell carcinoma, and combination treatment with SMYD2 inhibition and anticancer drugs significantly reduced the tumor volumes and weights, suggesting that SMYD2 could be a potential target for RCC treatment. Pi3K/mTOR inhibitor and EGFR repression played the coordinated role in animal survival and gefitinib-targeted therapy in malignant glioma. NGI-1, an inhibitor of oligosaccharyltransferase could block the interaction between MET and EGFR, resulting in increasing sensitivity to gefitinib and osimertinib in EGFR mutated NSCLC cells. AM-1-124 specifically targeted STAT3 and downregulated STAT3 phosphorylation overcame drug resistance in TKI-resistant chronic myeloid leukemia cells. TC-N19, which is the dual inhibitor of EGFR and cMET, degraded both proteins via ubiquitin proteasome pathway and overcome gefitinib resistance in NSCLC cells. Qi et al. found that the phosphorylation of ERK increased in gefitinib-resistant NSCLC cells and the inhibition of ERK phosphorylation reversed gefitinib resistance via suppressing autophagy in lung cancer. Knockdown of ubiquitin-specific peptidase 8 (USP8) decreased the phosphorylation of EGFR, c-MET, ERBB2, and ERBB3, and a synthetic USP8 inhibitor displayed a smaller tumor size and a reversed gefitinib resistance in H1975 CDX model. WZB117, a specific inhibitor of Glut1, significantly increased the 5-FU resistance and could be used as the potential treatment in patients with 5-FU-resistant colon cancers. Protein tyrosine phosphatase receptor J (PTPJR) was downregulated in human cervical tumor tissues and inhibition of PTPJR could have promoted the resistance to 5-FU through activating JAK1/STAT3 pathway. Histone methyltransferase NSD2 mediated BCL-2 and SOX2 H3K36me2 modification and activated the levels of p-ERK and p-AKT in osteosarcoma. Knockdown of NSD2 induced cell apoptosis and led to the enhancing sensitivity of osteosarcoma to cisplatin. WP1130, the USP9x inhibitor, induced the degradation of transcription factor PBX1 and accelerated cell apoptosis in prostate cancer, which provided a new idea for prostate cancer treatment.

CONCLUSIONS AND FUTURE PERSPECTIVES}

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The dynamic intratumoral heterogeneity and the increased clonal repopulation are the main causes of cancer acquired resistance to platinum-based chemotherapy. Single-cell RNA-seq (scRNA-seq), the technology which allows transcriptomic analysis in individual cells, can dissect the heterogeneity and subpopulations in tumor microenvironment during cancer drug resistance. More attempts have been made to reveal the mechanism of drug resistance in cancers by scRNA-seq. For example, scRNA-seq from paclitaxel-sensitive and -resistant esophageal squamous cell carcinoma (ESCC) identified the subpopulations of paclitaxel-resistant ESCC cells, and research on the mechanism revealed the carfilzomib, a proteasome inhibitor, could reverse the paclitaxel resistance via activating the HIF-1 pathway. The transcriptome mapping of cisplatin-resistant tumor cells by scRNA-seq uncovered a novel gene COX7B, and inhibition of COX7B reduced the sensitivity of cisplatin, which provided the valuable insights into chemosensitivi-
An era of single-cell omics has arrived, and the future clinical applications based on epitranscriptomics and epiproteomics are very promising: (i) single-cell multiple omics sequencing technique can be used widely to analyze the transcriptome, proteome, epitranscriptome, and epiproteome simultaneously at the single-cell level in drug resistance cancer cells, which allows us to reveal the unknown mechanisms and targets; 220,221 (ii) personalized single-cell sequencing provides comprehensive clues to optimize the therapeutic strategy against relapsing cancers; 222 and (iii) application of single-cell sequencing on tumor liquid biopsy can surveil and prevent the drug-resistant events during therapeutic treatment. 225

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ADDITIONAL INFORMATION

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REFERENCES

1. Choi E. K. et al. Body mass index and 20 specific cancers: re-analyses of dose-response meta-analyses of observational studies. Ann. Oncol. 29, 749–757 (2018).
2. Bray F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 68, 394–424 (2018).
3. Saitoh M. Involvement of partial EMT in cancer progression. J. Biochem. 164, 257–264 (2018).
4. Ayati A. et al. A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. Bioorg. Chem. 99, 103811 (2020).
5. Sio, T. T., Ko, J., Gudena, V. K., Verma, N. & Chaudhary, U. B. Chemotherapeutic and targeted biological agents for metastatic bladder cancer: a comprehensive review. Int. J. Urol. 21, 630–637 (2014).
6. Holohan, C., Van Schaeybroeck, S., Longley, D. B. & Johnston, P. G. Cancer drug resistance: an evolving paradigm. Nat. Rev. Cancer 13, 714–726 (2013).
7. Liu et al. Long non-coding RNAs regulate drug resistance in cancer. Mol. Cancer 19, 54 (2020).
8. Kang, K. A. & Hyun, J. W. Oxidative stress, Nrf2, and epigenetic modification contribute to anticancer drug resistance. Toxicol. Res. 33, 1–5 (2017).
9. Dominissini, D. & Rechavi, G. Epitranscriptome regulation. Nat. Struct. Mol. Biol. 28 (2018).
10. Stram, A. R. & Payne, R. M. Post-translational modifications in mitochondria: protein signaling in the powerhouse. Cell Mol. Life Sci. 73, 4063–4073 (2016).
11. Rape M. Ubiquitylation at the crossroads of development and disease. Nat. Rev. Mol. Cell Biol. 19, 59–70 (2018).
12. Han, Z. J., Feng, Y. H., Gu, B. H., Li, Y. M. & Chen, H. The post-translational modification, SUMOylation, and cancer (Review). Int. J. Oncol. 52, 1081–1094 (2018).
13. Bannister, A. J. & Kouzarides, T. Regulation of chromatin by histone modifications. Cell Res. 21, 381–395 (2011).
14. Kelly, A. D. & Isaa, J. J. The promise of epigenetic therapy: reprogramming the cancer epigenome. Curr. Opin. Genet. Dev. 42, 68–77 (2017).
15. Ciesielski O. et al. The epigenetic pro-

Epitranscriptomics and epiproteomics in cancer drug resistance:... Song et al.
14. Zhang H. D. et al. Exosome: a novel mediator in drug resistance of cancer cells. *Epigenomics* 10, 1499–1509 (2018).
15. Mashouli L. et al. Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. *Mol. Cancer* 18, 75 (2019).
16. Qin X. et al. Exosomal miR-196a derived from cancer-associated fibroblasts confers cisplatin resistance in head and neck cancer through targeting CDKN1B. *Mol. Cancer* 20, 12 (2019).
17. Wang D. et al. MicroRNA-936 induces cell cycle arrest and inhibits glioma cell proliferation by targeting CKS1. *Am. J. Cancer Res.* 7, 2131–2143 (2017).
18. Zhou, X. & Tao, H. Overexpression of microRNA-936 suppresses non-small cell lung cancer cell proliferation and invasion via targeting E2F2. *Exp. Ther. Med.* 16, 2696–2702 (2018).
19. Lin X. J. et al. miR-336 suppresses cell proliferation, invasion, and drug resistance of laryngeal squamous carcinoma cells and targets GPR78. *Front. Oncol.* 10, 60 (2020).
20. Zhang Y. et al. NOTCH3 overexpression and postranscriptional regulation by miR-150 were associated with EGFR-TKI resistance in lung adenocarcinoma. *Oncol. Res.* 27, 751–761 (2019).
21. Bach D. H. et al. BMP4 upregulation is associated with acquired drug resistance and fatty acid metabolism in EGFR-mutant non-small-cell lung cancer cells. *Mol. Ther. Nucleic Acids* 12, 817–828 (2018).
22. Yang, L., Zhang, L., Lu, L. & Wang, Y. miR-214-3p regulates drug resistance and apoptosis in retinoblastoma cells by targeting ABCB1 and XIAP. *Onco Targets Ther.* 13, 803–811 (2020).
23. Tao L. et al. MiR-451a attenuates doxorubicin resistance in lung cancer via suppressing epithelialmesenchymal transition (EMT) through targeting c-Myc. *Biomed. Pharmacother.* 125, 109962 (2020).
24. Han T. et al. miR-552 regulates liver tumor-initiating cell expansion and sorafenib resistance. *Mol. Ther. Nucleic Acids* 19, 1073–1085 (2020).
25. Bester A. C. et al. An integrated genome-wide CRISPRa approach to functionalize IncRNAs in drug resistance. *Cell* 173, 649–654.e20 (2019).
26. Lu Y. et al. IncRNA MIR100HG-derived mir-100 and miR-125b mediate cetuximab resistance via Wnt/beta-catenin signaling. *Nat. Med.* 23, 1331–1341 (2017).
27. Kong X. et al. Analysis of IncRNA, miRNA and miRNA-associated ceRNA networks and identification of potential drug targets for drug-resistant non-small cell lung cancer. *J. Cancer* 11, 3357–3368 (2020).
28. Zhang J. et al. A novel long non-coding RNA, MSTRG.S1053.2 regulates cisplatin resistance by sponging the mir-432-5p in non-small cell lung cancer cells. *Front. Oncol.* 10, 215 (2020).
29. Zhang, Z., Li, M. & Zhang, Z. IncRNA MALAT1 modulates oxaliplatin resistance of gastric cancer via sponging miR-22-3p. *Onco Targets Ther.* 13, 1334–1354 (2020).
30. Sun, H., Sun, Y., Chen, Q. & Xu, Z. LncRNA KCNQ1OT1 contributes to the poor survival of colorectal cancer patients. *Am. J. Cancer Res.* 9, 22–28 (2019).
31. Zhang, Z. F. et al. TXNDC17 promotes paclitaxel resistance via inactivating autophagy in ovarian cancer. *Autophagy* 11, 225–238 (2015).
32. Sisinni L. et al. Endolysosomal reticular stress and unfolded protein response in breast cancer: the balance between apoptosis and autophagy and its role in drug resistance. *Int. J. Mol. Sci.* 20, 857 (2019).
33. Li Y. J. et al. Autophagy and multidrug resistance in cancer. *Chin. J. Cancer* 36, 52 (2017).
34. Smith, A. G. & Macleod, K. F. Autophagy, cancer stem cells and drug resistance. *J. Pathol.* 247, 708–718 (2019).
35. Yang Y. et al. Silencing of LncRNA-HOTAIR decreases drug resistance of non-small cell lung cancer cells by inactivating autophagy via suppressing the phosphorylation of ULK1. *Biochem. Biophys. Res. Commun.* 497, 1003–1010 (2018).
36. Zhang W. et al. Long non-coding RNA LINCO0160 functions as a decoy of microRNA-132 to mediate autophagy and drug resistance in hepatocellular carcinoma via inhibition of PI3K/AKT. *Cancer Lett.* 478, 22–33 (2020).
37. Zhang, Y. F., Li, C. S., Zhou, Y. & Lu, X. H. Propofol facilitates cisplatin sensitivity via IncRNA MALAT1/miR-30e/ATG5 axis through suppressing autophagy in gastric cancer. *Life Sci.* 248, 117611 (2020).
38. Yifan H. et al. Long noncoding RNA MALAT1 regulates autophagy associated chemoresistance via miR-23b-3p sequestration in gastric cancer. *Mol. Cancer* 16, 174 (2017).
39. Yuan P. et al. The HIF-Zalpha-MALAT1-miR-216b axis regulates multi-drug resistance of hepatocellular carcinoma cells via modulating autophagy. *Biochem. Biophys. Res. Commun.* 478, 1067–1073 (2016).
40. Wang X. et al. LncRNA SNHG6 promotes chemoresistance via ULK1-induced autophagy by sponging miR-26a-5p in colorectal cancer cells. *Cell Chem. Biol.* 19, 234 (2012).
41. Li W. et al. LncRNA SNHG1 contributes to sorafenib resistance by activating the Akt pathway and is positively regulated by miR-21 in hepatocellular carcinoma cells. *J. Exp. Clin. Cancer Res.* 38, 183 (2019).
112. Zhang, X., Zhao, P., Wang, C. & Xin, B. SNHG14 enhances gemicitabine resistance by sponging miR-101 to stimulate cell autophagy in pancreatic cancer. Biochem. Biophys. Res. Commun. 510, 508–514 (2019).

113. Tang, Q. & Hann, S. S. Biological roles and mechanisms of circular RNA in human cancers. Onco Targets Ther. 13, 2067–2092 (2020).

114. Huang X. et al. Circular RNA AKT3 upregulates PKR1R1 to enhance cisplatin resistance in gastric cancer via miR-198 suppression. Mol. Cancer 18, 71 (2019).

115. Shang J. et al. CircRNAP33 contributes to drug resistance in acute myeloid leukemia through regulation of autophagy. Leuk. Res. 85, 106198 (2019).

116. Shang J. et al. CircRNAP33 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p-XIAP axis. Exp. Hematol. 70, 42–54.e3 (2019).

117. Lai M. et al. Hsa_circ_0079662 induces the resistance mechanism of the chemotherapeutic drug oxaplatin through the TNF-alpha pathway in human colon cancer cells. J. Cell Mol. Med. 24, 5021–5027 (2020).

118. Liu F. et al. Circular RNA EIF6 (Hsa_circ_0060060) sponges miR-144-3p to promote the cisplatin-resistance of human thyroid carcinoma cells by autophagy regulation. Aging 10, 3806–3820 (2018).

119. Zhang S. et al. circCLES1R1 (Hsa_circ_0063809) contributes to paclitaxel resistance of ovarian cancer cells by regulating FOX2R2 expression via miR-1252. Mol. Ther. Nucleic Acids 19, 718–730 (2020).

120. Dong Y. et al. Circ006305 regulates cisplatin resistance of non-small cell lung cancer via positively modulating STAT3 by sponging miR-296-5p. Life Sci. 239, 116984 (2021).

121. Li X. et al. Hsa_circ_0002483 inhibited the progression and enhanced the Taxol sensitivity of non-small cell lung cancer by targeting miR-182-5p. Cell Death Dis. 10, 953 (2019).

122. Sang Y. et al. circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer. Mol. Ther. 27, 1638–1652 (2019).

123. Liang Y. et al. circKDMAC suppresses tumor progression and attenuates doxorubicin resistance by regulating miR-548p/PBLD axis in breast cancer. Onco-gene 38, 6850–6866 (2019).

124. Walko, C. M. & Lindley, C. Capecitabine: a review. M. Cell Mol. Proteom. 6, 4749 (2008).

125. Longley, D. B., Harkin, D. P. & Johnston, P. G. 5-fluorouracil: mechanisms of action and clinical strategies. Nat. Rev. Cancer 3, 330–338 (2003).

126. Li, W. & Yue, H. Thymidine phosphorylase: a potential new target for treating cancer. Cancer Cell. Mol. Med. 24, 701–707 (2019).

127. Chung T. et al. Dihydropyrimidine dehydrogenase is a prognostic marker for chemotherapeutic drug resistance. Exp. Hematol. 43, 174–181 (2015).

128. Lu Y. et al. Epidermal growth factor receptor (EGFR) ubiquitination as a mechanism of acquired resistance escaping treatment by the anti-EGFR monoclonal antibody cetuximab. Cancer Res. 67, 8240–8247 (2007).

129. Molina M. A. et al. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res. 61, 4744–4749 (2001).

130. Gijzen M. et al. HER2 phosphorylation is maintained by a PKB negative feedback loop in response to anti-HER2 herceptin in breast cancer. PLoS Biol. 8, e1000563 (2010).

131. Huang Z. et al. The E3 ubiquitin ligase NEDD4 negatively regulates HER3/Erbb3 level and signaling. Oncogene 34, 1105–1115 (2015).

132. VanMeter A. J. et al. Laser capture microdissection and protein microarray analysis of human non-small cell lung cancer: differential epidermal growth factor receptor (EGFR) phosphorylation events associated with mutated EGFR compared with wild type. Mol. Cell. Proteom. 7, 1902–1924 (2008).

133. Sergina N. V. et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 445, 437–441 (2007).

134. Canfield K. et al. Receptor tyrosine kinase ERBB4 mediates acquired resistance to ERBB2 inhibitors in breast cancer cells. Cell Cycle 14, 648–655 (2015).

135. Salehan, M. R. & Morse, H. R. DNA damage repair and tolerance: a role in chemotherapeutic drug resistance. Br. J. Biomed. Sci. 70, 31–40 (2013).

136. Zhang Y. et al. Human DNA polymerase kappa synthesizes DNA with extraordinary low fidelity. Nucleic Acids Res. 28, 4174–4176 (2000).

137. Albertella, M. R., Lau, A. & O’Connor, M. J. The overexpression of specialized DNA polymerases in cancer. DNA Repair 4, 583–593 (2005).

138. Topalis, D., Gillemot, S., Snoeck, R. & Andrei, G. Distribution and effects of amino flux transporter multidrug resistance-associated proteins 5 affects sensitivity of pancreatic cancer cell lines to the nucleoside analogue gemcitabine. Cell surface death receptor signaling and normal and cancer cells. Semin. Cancer Biol. 13, 135–147 (2003).

139. Mansoori, B., Mohammadi, A., Davudian, S., Shirjng, S. & Baradaran, B. The different mechanisms of cancer drug resistance: a brief review. Adv. Pharm. Bull. 7, 339–348 (2017).

140. Wu K. et al. Synthesis and evaluation of dibenzothiophene analogues as Pin1 inhibitors for cervical cancer therapy. ACS Omega 4, 9226–9234 (2019).
172. Campbell, K. J. & Tait, S. W. G. Targeting BCL-2 regulated apoptosis in cancer. \emph{Open Biol.} \textbf{8}, 180002 (2018).

173. Wertz I. E. et al. Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. \emph{Nature} \textbf{471}, 110–114 (2011).

174. Kelle J. et al. Phosphorylation switches \textit{Bax} from promoting to inhibiting apoptosis thereby increasing drug resistance. \emph{EMBO Rep.} \textbf{19}, e45235 (2018).

175. Jimenez P. R. et al. Antigen-specific primed cytotoxic T cells eliminate tumour cells in vivo and prevent tumour development, regardless of the presence of anti-apoptotic mutations conferring drug resistance. \emph{Cell Death Differ.} \textbf{25}, 1536–1548 (2018).

176. Hu X. et al. Cul4 E3 ubiquitin ligase regulates ovarian cancer drug resistance by targeting the antitapoptotic protein BIRC3. \emph{Cell Death Dis.} \textbf{10}, 104 (2019).

177. Ganley I. G. et al. ULK1.ATG13.FIP200 complex mediates mTOR signaling and is essential for autophagy. \emph{J. Biol. Chem.} \textbf{284}, 12927–12935 (2009).

178. Spitzer, R., Cleves, A. E. & Jain, A. N. Surface-based protein binding pocket similarity. \emph{Proteins} \textbf{79}, 2746–2763 (2011).

179. Motono C. et al. SAHG, a comprehensive database of predicted structures of all human proteins. \emph{Nucleic Acids Res.} \textbf{39}, D487–D493 (2011).

180. Pópulo, H., Lopes, J. M. & Soares, P. The mTOR signalling pathway in human cancer. \emph{Int. J. Mol. Sci.} \textbf{13}, 1886–1918 (2012).

181. Ribatti, D., Tamma, R. & Annese, T. Epithelial-mesenchymal transition in cancer: a critical point of view. \emph{Oncogene} \textbf{37}, 3234 (2012).

182. Brabletz, T., Kalluri, R., Nieto, M. A. & Weinberg, R. A. EMT in cancer. \emph{Nat. Rev. Mol. Cell Biol.} \textbf{9}, 850–863 (2008).

183. Zhang K. et al. Lats2 kinase potentiates Snail1 activity by promoting nuclear retention upon phosphorylation. \emph{J. Biol. Chem.} \textbf{285}, 3184 (2010).

184. Thomson S. et al. Epithelial to mesenchymal transition is a determinant of radioresistance in pancreatic cancer cells. \emph{Cancer Biomark.} \textbf{17}, 179–189 (2015).

185. Zhou B. P. et al. Dual regulation of Snail by GSK-3beta-mediated phosphorylation and histone H3 deacetylation. \emph{Oncogene} \textbf{31}, 6666–6676 (2012).

186. Zhang K. et al. Lats2 kinase potentiates Snail1 activity by promoting nuclear retention upon phosphorylation. \emph{EMBO J.} \textbf{30}, 29–43 (2012).

187. Yang Z. et al. Pak1 phosphorylation of snail, a master regulator of epithelial-to-mesenchymal transition or beyond. \emph{Mol. Carcinog.} \textbf{58}, 201–211 (2019).

188. Cheng G. Z. et al. Twist transcriptionally up-regulates AKT2 in breast cancer cells leading to increased migration, invasion, and resistance to paclitaxel. \emph{Cell Death Discov.} \textbf{5}, 121 (2019).

189. Vesuna F. et al. Twist contributes to hormone resistance in breast cancer by downregulating estrogen receptor-\textalpha. \emph{Oncogene} \textbf{31}, 3233–3242 (2012).

190. Taketo R. et al. The epithrapsin-mRNA6 writer METTL3 promotes chemo- and radioresistance in pancreatic cancer cells. \emph{Int. J. Oncol.} \textbf{52}, 621–629 (2018).

191. Zhu, J., Tao, L. & Jin, L. MicroRNA5063p reverses gefitinib resistance in non-small cell lung cancer by targeting Ysassociated protein 1. \emph{Mol. Med. Rep.} \textbf{19}, 1331–1339 (2019).

192. Wang, Y., Xiao, W., Cai, Z., Jin, S. & Li, T. miR-1269b drives cisplatin resistance of human non-small cell Lung cancer via modulating the PTEN/Pi3K/AKT signaling pathway. \emph{Onco Targets Ther.} \textbf{13}, 109–118 (2020).

193. Zhu X. et al. miR-186 regulation of Twist1 and ovarian cancer sensitivity to cisplatin. \emph{Oncogene} \textbf{35}, 323–332 (2016).

194. Fu Q. et al. miR-20B reduces FS resistance by suppressing the ADAM9/EGFR signaling pathway in colon cancer. \emph{Oncol. Rep.} \textbf{37}, 123–130 (2017).

195. Wang L. et al. MiR-153 inhibits the resistance of lung cancer to gefitinib via modulating expression of ABCG1. \emph{Cancer Biomark.} \textbf{25}, 361–369 (2019).

196. Hu M. et al. IncRNA CCAT1 is a biomarker for the proliferation and drug resistance of esophageal cancer via the miR-143/PLK1/BUBR1 axis. \emph{Mol. Carcinog.} \textbf{58}, 2207–2217 (2019).

197. Liu H. et al. Knockdown of long non-coding RNA UCA1 increases the tamoxifen sensitivity of breast cancer cells through Inhibition of Wnt/beta-catenin pathway. \emph{PLoS One} \textbf{11}, e0168406 (2016).

198. Zhu J. et al. Knockdown of long non-coding RNA XIST inhibited doxorubicin resistance in colorectal cancer by upregulation of miR-124 and downregulation of SGK1. \emph{Cell Physiol. Biochem.} \textbf{51}, 113–128 (2018).

199. Sainesab M. et al. SNHG15 is a bifunctional MYC-regulated noncoding locus encoding an lncRNA that promotes cell proliferation, invasion and drug resistance in colorectal cancer by interacting with \textit{AIF}. \emph{J. Exp. Clin. Cancer Res.} \textbf{38}, 172 (2019).

200. Luo Y. et al. CircRNA_101505s sensitizes hepatocellular carcinoma cells to cisplatin by splicing mIR-103 and promotes oxidized-nitro domain-containing protein 1 expression. \emph{Cell Death Discov.} \textbf{5}, 121 (2019).

201. Yan L. et al. Inhibition of SMYD2 suppresses tumor progression by down-regulating microRNA-125B and attenuates multi-drug resistance in renal cell carcinoma. \emph{Theranostics} \textbf{9}, 8377–8391 (2019).