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REVIEW ARTICLE

The mechanism of ncRNA in trastuzumab resistance in HER2-positive tumors

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Abstract

Human epidermal growth factor receptor-2 (HER2) is an essential biomarker in oncology. It is highly expressed in many tumors, especially in breast cancer and gastric cancer, and is associated with the malignant progression of tumors. Trastuzumab is a targeted drug for HER2-positive tumors, which can improve the efficacy of HER2-positive tumors, initiate precise treatment of HER2-positive tumors, and play an essential role in first-line therapy and second-line therapy. However, resistance to Trastuzumab is a limiting factor for its efficacy and a necessary factor for short patient survival and poor prognosis. The resistance mechanism to trastuzumab is complex, and non-coding RNA (ncRNA), a type of RNA that does not encode genes, mediates resistance, and plays important roles in of trastuzumab resistance. In clinical practice, ncRNA can be a biomarker for tumor progression, prognosis, and trastuzumab resistance. This article systematically summarizes the key mechanisms of ncRNA resistance to trastuzumab in HER2-positive tumors and its clinical application potential. Especially in this article, for the first time, ncRNA is integrated to regulate of trastuzumab resistance through epigenetic modification crosstalk, insulin-like growth factor 1 receptor (IGF1R) targets, exosome delivery, and ceRNA network regulation aimed to provide insights and references for basic research, drug development, and biomarker determination of trastuzumab resistance in HER2-positive tumors.

Keywords ncRNA · Trastuzumab · Drug resistance · Cancer · Mechanism

Introduction

As a member of the epidermal growth factor receptor (EGFR) family, HER2 undergoes gene amplification in 20–30% of breast cancer cases and 10–20.2% of gastric cancer cases, and its abnormal activation of tyrosine kinase activity drives the tumor malignant process [1, 2]. In targeted therapy for HER2-positive tumors, trastuzumab, as a key therapeutic drug, significantly improves patient prognosis, prolongs patient survival, but some HER2-positive patients have primary resistance, and initially sensitive patients often develop acquired resistance within 12 months of treatment [3]. The complexity of trastuzumab's resistance mechanism is reflected in multiple biological processes, including structural variation/reduction of HER2 receptors, reactivation of downstream signaling pathways such as PI3K/AKT/mTOR, enhanced epithelial–mesenchymal transition (EMT), maintenance of tumor stem cell characteristics, and abnormal expression of microRNA (miRNA) [4]. Clinical translational studies have revealed the stability, detectability, and strong correlation between non-coding RNA (ncRNA) and drug

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resistance phenotype in biological samples such as serum and tissue [5]. In recent years, ncRNA as a key participant in gene expression regulatory networks, has made breakthrough progress in the research of tumor drug resistance mechanisms. Its unique biological characteristics and clinical translation potential offer promising new perspective for solving the problem of trastuzumab resistance [6]. ncRNA forms multidimensional interactions with drug resistance mechanisms through epigenetic regulatory networks [7]. miRNA, as a 19-25nt short-chain regulatory molecule, achieves post-transcriptional regulation by combining the seed sequence with the target mRNA 3'UTR [8]. Its function has significant tumor type specificity, which can not only act as an oncogene to promote drug resistance but also as an anti-tumor gene to enhance drug sensitivity [9]. Long non-coding RNA (lncRNA) with a length exceeding 200 nucleotides can dynamically regulate gene expression networks through chromatin remodeling, transcriptional interference, and ceRNA. For example, the lncRNA miRNA sponge effect can alleviate miRNA's inhibitory effect on oncogenes [10]. Circular RNA (circRNA) covalently closes a circular structure without a 5 'cap and 3' tail and has high stability. It serves as a miRNA sponge, regulates transcription or translation, and participates in protein interactions [11]. Notably, this review is the first to systematically integrate the multidimensional crosstalk among ncRNA-mediated epigenetic modifications (e.g., m6A, H3K27ac), competitive endogenous RNA (ceRNA) networks, IGF1R signaling, and exosome-mediated cellular communication involving ncRNA in driving trastuzumab resistance. By integrating basic research data and clinical trial evidence, the aim is to identify the key ncRNA mechanisms of HER2-positive trastuzumab resistance and promote the application of ncRNA in clinical diagnosis and drug therapy.

Mechanism of ncRNA resistance to trastuzumab in HER2-positive tumors

ncRNA targets PI3K/AKT signaling pathway to mediate drug resistance

The PI3K/AKT signaling axis, serving as the central molecular hub for anti-HER2 therapeutic resistance, orchestrates critical oncogenic processes including neoplastic proliferation, apoptotic evasion, and metastatic dissemination through intricate crosstalk with miRNA regulatory networks [12, 13]. These non-coding RNAs predominantly modulate therapeutic responsiveness to trastuzumab through multiple mechanisms via PI3K/AKT pathway. miR-542-3p induces mitochondrial apoptosis pathways via PI3K-AKT axis suppression, where genetic ablation of this miRNA compromises trastuzumab-mediated G1/S phase arrest and diminishes drug sensitivity [14]. miR-141 directly targets ERBB4's 3'-UTR to attenuate AKT phosphorylation, effectively reversing apoptotic defects in treatment-refractory cellular populations [15]. Comparative genomic analyses by Rao et al. revealed significant miR-126 downregulation in trastuzumab-resistant clones cells (SKBR3/TR, BT474/TR), concomitant with PIK3R2 (PI3K regulatory subunit) overexpression. This molecular rewiring enhances AKT activation, accelerates migratory capacity, and establishes drug tolerance [16]. Notably, ectopic miR-21 expression in HER2 + breast cancer models confers therapeutic resistance through PTEN suppression and AKT signaling. Restoration of PTEN-mediated regulation via 3'UTR modification re-sensitizes resistant cells to trastuzumab-induced growth inhibition [17]. Complementary studies demonstrated miR-21's dual role in modulating IL-6/STAT3/NF-κB and PI3K pathway activation, while maintaining EMT programs and sculpting immunosuppressive microenvironments in HER2 + malignancies [18]. HOX transcript antisense RNA (HOTAIR) represents the first identified long non-coding RNA (lncRNA) to modulate gene expression through transcriptional regulatory mechanisms [19]. It is found to be highly expressed in various cancers and correlates with tumor grading and poor prognosis, facilitating tumor growth and resistance to treatment [20]. When HOTAIR was silenced in SKBR3-TR cells, a reduction in p-AKT, p-MAPK, and CyclinD1 levels was observed, accompanied by an elevation in PTEN expression. By contrast, the expression of PIK3CA, AKT, mTOR, MAPK, and the HER2 receptor remained largely unaltered. These findings imply that HOTAIR promotes PTEN upregulation, activates the PI3K/AKT/mTOR and MEK/MAPK signaling cascades, and contributes to the G1-to-S phase transition [21]. Furthermore, HOTAIR-mediated transcriptional reprogramming elevates TGF-β/Snail/Vimentin, while suppressing E-cadherin, establishing pro-metastatic EMT states that exacerbate drug tolerance [21]. Long non-coding RNA (lncRNA) can modulate the PI3K/AKT signaling pathway by functioning as miRNA sponges, thereby driving tumor progression [22]. For example, LINC00665 upregulates SERPINE1 expression through sequestration of miR-199b-5p, which in turn activates the PI3K/AKT pathway and facilitates gastric cancer development as well as trastuzumab resistance [23]. Mechanistic studies reveal that circCDYL2 stabilizes GRB7 protein by inhibiting ubiquitination-mediated degradation and strengthens its association with FAK, thereby triggering downstream AKT and ERK1/2 signaling to maintain the drug-resistant phenotype [24].

Thus, studies suggest that the activation of the PI3K/AKT signaling axis by ncRNA may be a key driving factor for tumor proliferation, invasion, and apoptosis in trastuzumab

resistance. These findings provide a theoretical basis for further investigation into combining PI3K inhibitors with trastuzumab (Fig. 1)

ncRNA mediates drug resistance through apoptosis

The three primary morphological categories of cancer cell death are apoptosis, autophagy, and necrosis. Tumor proliferation often relies on evading the normal apoptotic program [25]. Apoptosis is regulated through two distinct pathways: an extrinsic pathway that activates cysteine-aspartate protease (Caspase) signaling via death receptors, and an intrinsic pathway where mitochondrial release of cytochrome C under cellular damage or stress triggers downstream Caspases (e.g., Caspase-3) [26].

Tumor cells' resistance to apoptosis enables them to survive drug-induced killing, a key mechanism underlying trastuzumab resistance [27]. Besides miR-21 that targets PTEN, the oncogenic miR-221 also contributes to trastuzumab resistance and the metastasis of HER2-positive breast cancer. It achieves this by targeting PTEN, which inhibits cell apoptosis [28]. Dolap çI et al. demonstrated via microarray analysis that miR-216b-5p overexpression induces late-stage apoptosis/necrosis in SKBR3-resistant cells through targeted inhibition of signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 9 (IRF9), and protein kinase R (PKR) [29]. In a separate regulatory mechanism, miR-223 suppresses trastuzumab-induced apoptosis in gastric cancer cells by downregulating FBXW7, a component of the E3 ubiquitin ligase complex; conversely, FBXW7 re-expression reverses this resistant phenotype [30]. Trastuzumab resistance is also linked to circular RNA (circRNA)-modulated cell death pathways. Notably, circVDAC3 maintains HSPB1 protein stability by inhibiting its ubiquitination and degradation through direct binding, thereby counteracting trastuzumab-induced oxidative stress and ferroptosis. The small molecule paritaprevir disrupts the circVDAC3–HSPB1 interaction to reverse drug resistance [31]. Additionally, circBGN promotes SLC7A11 deubiquitination via the OTUB1/SLC7A11 axis, further suppressing

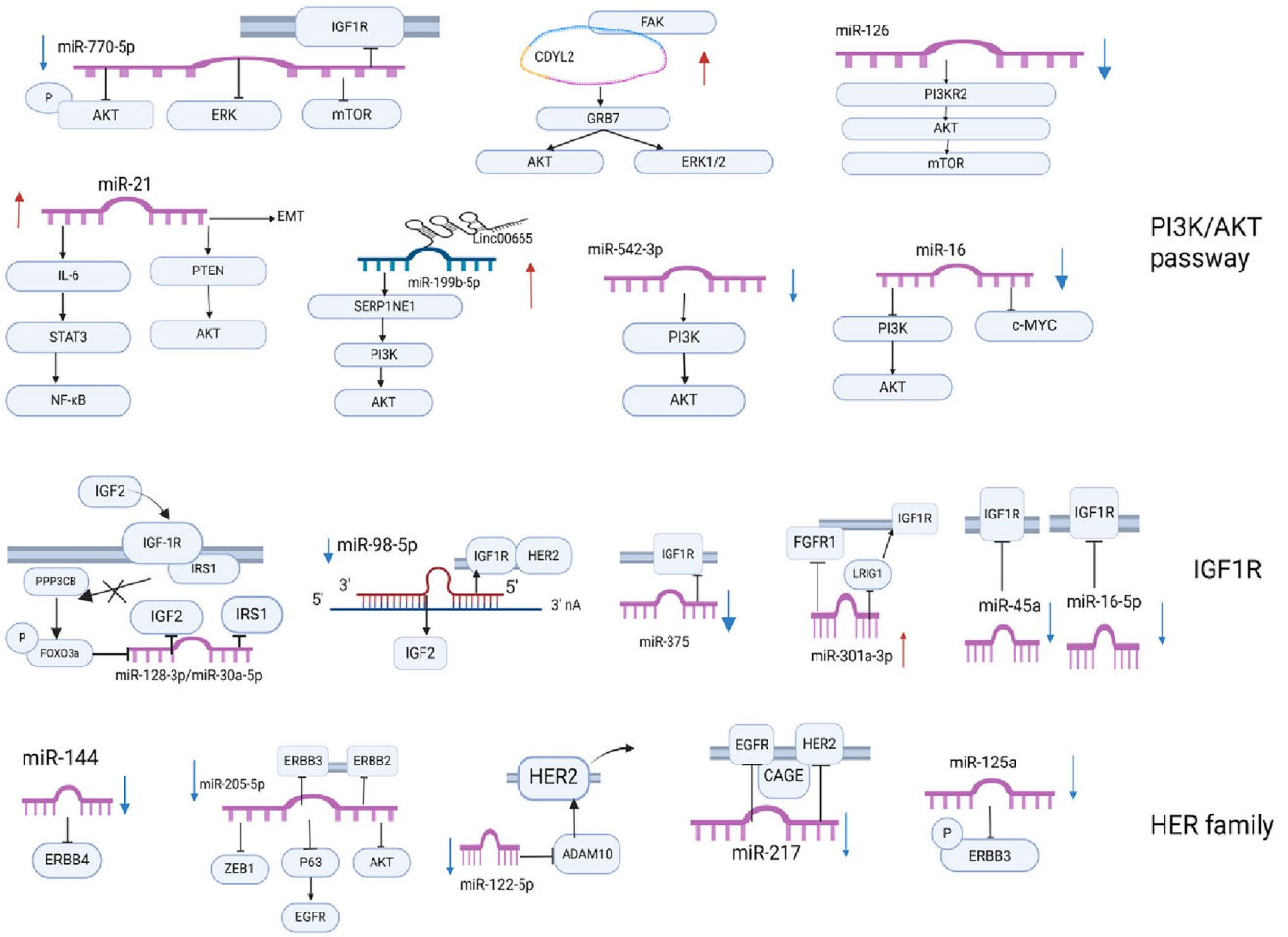

Fig. 1 ncRNA affects trastuzumab resistance by targeting the PI3K/AKT pathway, HER family, IGF1R

ferroptosis and enhancing resistance [32]. These findings collectively may illustrate the complex molecular networks governing tumor cell death by ncRNA to regulate resistance (Fig. 2).

ncRNA mediates drug resistance through proliferation

Tumor proliferation refers to the formation of tumor tissue by tumor cells through abnormal cell division and proliferation processes [33]. Tumor cells break through the limitations of normal cell proliferation by acquiring abnormal growth and division abilities, thereby achieving tumor growth and spread [34]. Inhibiting proliferation enhances the inhibitory effect of drugs on tumor cells.

Cell cycle E2 (CCNE2) belongs to the cyclin family and reaches its peak in the G1-S phase [35]. miR-30b reduces HER2 + acquired trastuzumab resistance in breast cancer by targeting the inhibition of CCNE2 expression and tumor growth [36]. miR-135b-5p directly targets cyclin D2 to block the G0/G1 phase, significantly enhancing the antiproliferative effect of trastuzumab, inducing apoptosis, and inhibiting cell metastasis [37]. Antisense oligonucleotides targeting miR-21 can antagonize its activity in antibody-treated cells, inducing growth arrest, proliferation inhibition, and G1/S cell cycle blockade. This mechanism re-sensitizes drug-resistant cells to the therapeutic effects of trastuzumab [17]. In nearly 50% of HER2-positive breast tumors, the oncogenic HER2 Δ16 isoform coexists with wild-type HER2. In MCF-7/HER2 Δ16 cells, the tumor-suppressive miR-7 is downregulated compared to parental MCF-7 cells. Restoring miR-7 expression in these cells leads to G1 phase cell cycle arrest, reduced colony formation ability, and decreased migration activity, reverting them to a phenotype similar to parental MCF-7 cells. Mechanistically, miR-7 inhibits tumor cell invasion and suppresses the proliferation of MCF-7/HER2 Δ16 cells by targeting EGFR and inactivating Src kinase, thereby enhancing their sensitivity to trastuzumab [38]. Cancer stem cells (CSCs) exhibit self-renewal capacity, indefinite proliferation potential, and the ability to maintain

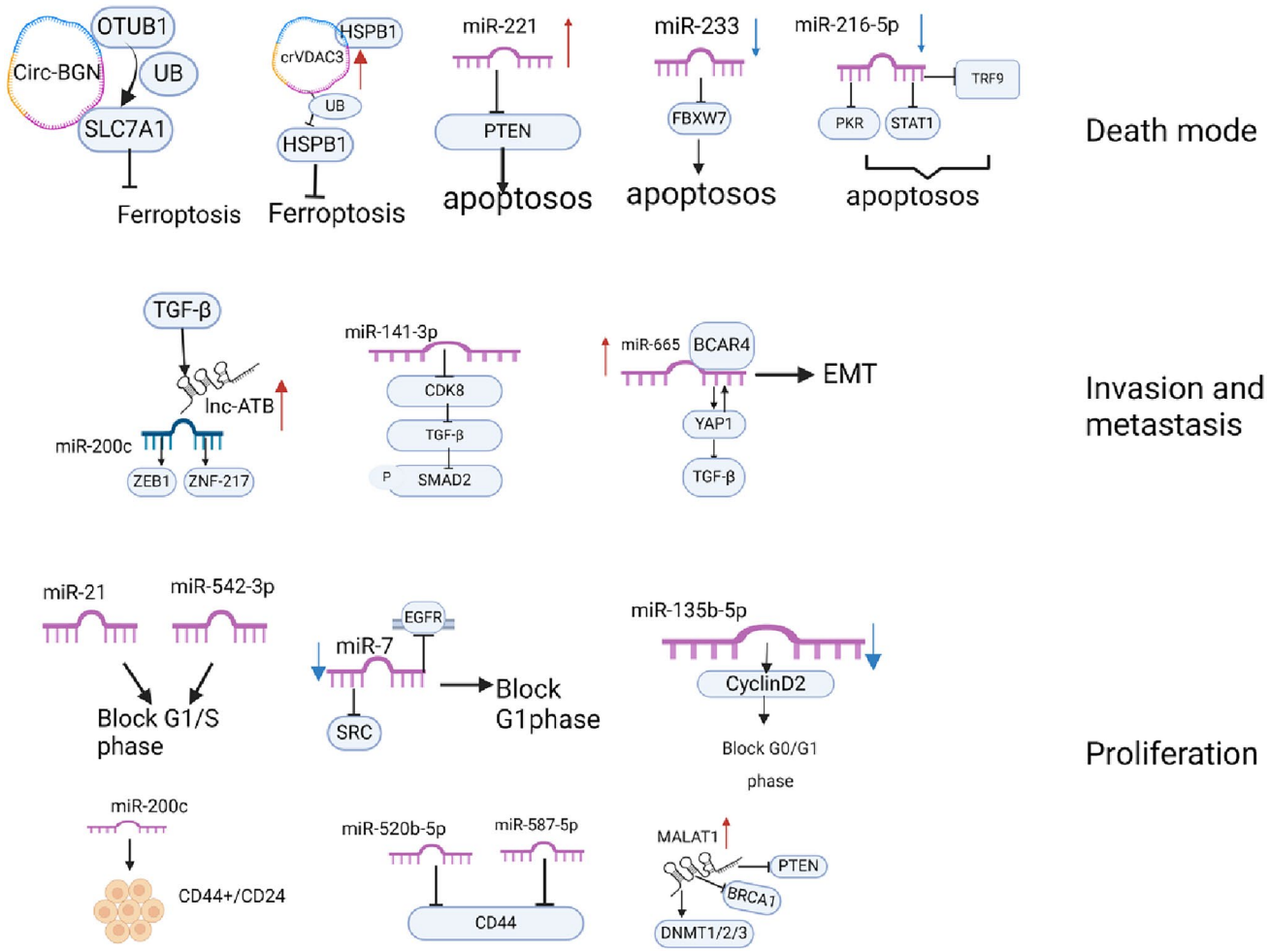

Fig. 2 ncRNA affects trastuzumab resistance by targeting invasion, metastasis, proliferation, and death

tumor cell populations, driving tumor initiation, progression, and metastasis [39]. CD44, a well-recognized CSC marker, is pivotal in mediating tumor metastasis, recurrence, and drug resistance [40]. Specifically, miR-200c significantly reduces the formation of CD44 + CD24 − mammary spheroids—a hallmark of CSC activity. When combined with trastuzumab, this miRNA enhances apoptosis and suppresses proliferation in both SKBR3 and SKBR3-S cell lines, demonstrating its role in dampening CSC-like phenotypes. Mechanistically, miR-200c promotes trastuzumab sensitivity in HER2 + cells and CSCs by inhibiting stemness-associated traits [41]. Long non-coding RNAs (lncRNAs) exhibit a complex three-dimensional structure, which contributes to their dynamic nature and multifunctional capabilities, including roles in cellular proliferation [42]. Long non-coding RNAs (lncRNAs) exhibit a complex three-dimensional structure, which contributes to their dynamic nature and multifunctional capabilities, including roles in cellular proliferation. MALAT1 is widely recognized as a lncRNA that facilitates metastasis and is often overexpressed in various tumors. Yang et al. [43] demonstrated that MALAT1 expression is markedly upregulated in HER2-positive breast cancer cell lines and clinical tissues both in vitro and in vivo studies showed that silencing MALAT1 inhibits the proliferation of HER2-positive breast cancer cells. Mechanistically, shRNA-mediated MALAT1 knockdown results in decreased expression of DNMT1, DNMT3a, and DNMT3b, accompanied by increased levels of BRCA1 and PTEN. These findings suggest that MALAT1 plays an important role in promoting tumorigenesis and reducing cellular responsiveness to Herceptin in HER2-positive breast cancer.

ncRNA affects tumor invasion, metastasis, and drug resistance by targeting TGF-β

Studies have shown that transforming growth factor beta (TGF-β) triggers the SMAD signaling cascade, which subsequently promotes the expression of genes involved in epithelial–mesenchymal transition (EMT) [44]. As a critical biomarker for tumor invasion and metastasis, EMT plays a pivotal role in conferring drug resistance to neoplastic cells [45]. Shi et al. [46] demonstrated that TGF-β-activated long non-coding RNA (lncRNA) lncATB is markedly upregulated in both trastuzumab-resistant breast cancer cell lines and clinical tissues from patients. Mechanistically, lncATB exerts its function by competitively binding to miR-200c, leading to the upregulation of ZEB1 and ZNF-217. This process facilitates EMT progression, thereby contributing to trastuzumab resistance and enhancing the invasive metastatic potential of cancer cells [47]. Additionally, the miRNA-141-3p/CDK8 axis has been shown to inhibit tumor cell invasion and metastasis by downregulating TGF-β expression. Concurrently, this pathway restores trastuzumab sensitivity in breast cancer cells, highlighting its dual role in reversing drug resistance and suppressing metastatic capacity [48].

miRNA targeting insulin-like growth factor 1 receptor mediates drug resistance

In many tumors, binding of IGF2 to insulin-like growth factor 1 receptor (IGF1R) inhibits apoptosis and promotes cell proliferation [49]. The downregulation of miR-375 induces overexpression of IGF1R, reducing cell responsiveness to trastuzumab. This microRNA epigenetic inactivation leads to treatment failure. More importantly, inhibition of DNA methyltransferase and histone deacetylase effectively reactivated the expression of miR-375 in a treatment resistant cell model, revealing that epigenetic reprogramming is a feasible strategy for reversing acquired resistance phenotype [50]. Luo et al. [51] demonstrated that IGF2/IGF1R/IRS1 signal transduction is abnormally activated by destroying FOXO3a-miRNA(miR-128-3p and miR-30a-5p) negative feedback inhibition in herceptin-resistant breast cancer, promoting trastuzumab resistance. In cells resistant to Herceptin, the transcriptional inhibition of PPP3CB results in elevated levels of phosphorylated FOXO3a (p-FOXO3a), thereby disrupting the FOXO3a-miRNA negative feedback mechanism, leading to the upregulation of IGF2 and IRS1, and consequently enhancing drug resistance. Emerging evidence reveals miR-301a-3p's functional involvement in anti-HER2 therapeutic resistance through its dual regulatory effects on LRIG1 and FGFR1 suppression, which subsequently promote IGF1R activation [52]. In the tumor microenvironment, a cellular compartment-specific miRNA distribution pattern has been identified by Li et al., where miR-940 originates predominantly from malignant cells, while miR-45a, miR-16-5p, and miR-17-3p exhibit immune cell-derived characteristics. These differentially expressed miRNAs collectively orchestrate treatment insensitivity through distinct molecular interactions: miR-940 exerts regulatory effects on PTEN expression; miR-45a and miR-16-5p cooperatively modulate IGF1R; and miR-17-3p specifically influences SRC kinase activity, forming an interconnected network that sustains trastuzumab-refractory phenotypes [53].

miRNA targeting HER family mediates drug resistance

Trastuzumab, a monoclonal antibody that targets the HER2 receptor [54], warrants further investigation regarding its impact on the aberrant regulation of the HER family receptor network, particularly in the context of trastuzumab resistance. Overexpression of miR-770-5p leads to decreased phosphorylation of AKT and extracellular regulated protein kinases (ERK), indicating its inhibitory role in EGFR/

HER2 signaling. In addition, miR-770-5p downregulates the expression of insulin-like growth factor 1 (IGF1R) and mammalian target of rapamycin (mTOR). It shows that miR-770-5p can target to inhibit HER2/EGFR/IGF1R two-way crosstalk, reduce cell proliferation, and promote the sensitivity of trastuzumab-resistant breast cancer cells [55]. It is worth noting that the abnormal overexpression of miR-205-5p in breast cancer stem cells (BCSCs) will directly inhibit ERBB2 receptor, and indirectly affect EGFR signal pathway by regulating p63 transcription factor, forming miR-205/p63/EGFR regulatory axis, which may be an important molecular basis for the tolerance of targeted therapy [56]. As a tumor suppressor regulator, miR-122-5p exhibits various anti-cancer activities through different biological pathways. Of particular therapeutic significance is its ability to inhibit ADAM10-dependent shedding of HER2 extracellular domains, a molecular process closely associated with treatment resistance. This regulatory mechanism provides a promising pharmacological target for insensitivity to trastuzumab in clinical practice [57]. In a study conducted by Kim et al. [58], it was observed that the expression levels of miR-217 were diminished in Malme3MR cancer cells. CAGE establishes a feedback loop with miR-217, thereby amplifying the inhibitory effects of miR-217 on tumorigenicity, metastasis, and angiogenesis in cancer cells. This is achieved by diminishing the interaction between EGFR and HER2, which subsequently enhances sensitivity to trastuzumab.

ncRNA mediates drug resistance through epigenetic modification crosstalk

Long non-coding RNA (lncRNA) exhibits intricate and varied interactions with other epigenetic modifications, collectively influencing gene expression. For instance, the hnRNPL-LINC02273 complex enhances the expression of AGR2 by recruiting to its promoter region, thereby increasing the levels of local H3K4me3 and H3K27Ac, which in turn facilitates breast cancer metastasis [59]. Epigenetically modified long non-coding RNA (lncRNA) through m6A methylation, particularly the RNA modification-sensitive TP53TG1 transcript, exerts tumor-suppressive effects in gastric oncogenesis by post-transcriptionally regulating CIP2A mRNA stability [60]. ZNF649-AS1 is significantly overexpressed in trastuzumab-resistant HER2-positive breast cancer cells. This long non-coding RNA (lncRNA) regulates alternative splicing of EXOC7 by interacting with the PRPF8 splicing factor. Functionally, overexpression of the EXOC7-S isoform—mediated by ZNF649-AS1—potentiates trastuzumab resistance in HER2-positive breast cancer cell models [61]. Furthermore, ZNF649-AS1 can be upregulated through H3K27ac modifications, which are associated with the PTBP1 protein. This upregulation subsequently enhances the transcriptional activity and autophagy of the ATG5 gene, thereby contributing to the development of trastuzumab resistance [62]. Functionally characterized as an oncogenic lncRNA, AGAP2-AS1 has been implicated in malignant progression through its capacity to drive neoplastic growth and metastasis, with clinical correlative analyses revealing significant associations between elevated AGAP2-AS1 expression and adverse clinical outcomes in multiple cancer types [63]. Investigations led by Cai et al. [64]. demonstrated dysregulated expression patterns of this lncRNA in trastuzumab-resistant cellular models, establishing its functional involvement in anti-HER2 therapeutic resistance. Mechanistically, the METTL3/YTHDF2-dependent m6A modification machinery epigenetically upregulates AGAP2-AS1 via post-transcriptional stabilization, creating a pro-survival signaling loop that fundamentally sustains drug-refractory phenotypes in HER2-positive malignancies. AGAP2-AS1 can augment its expression through upstream m6A methylation and can also be secreted extracellularly by being incorporated into exosomes in a manner dependent on hnRNPA2B1. And AGAP2-AS1 can also be secreted extracellularly by being incorporated into exosomes in a manner dependent on hnRNPA2B1. Co-culturing exosomes containing AGAP2-AS1 with trastuzumab-sensitive cells resulted in a decrease in trastuzumab-induced cell death. Conversely, silencing AGAP2-AS1 in exosomes reversed this effect and restored sensitivity to trastuzumab [65, 66]. Additionally, circ-PPID influences HER2 stability through epigenetic mechanisms: circ-PPID acts as a protein-binding partner and binds to N-acetyltransferase 10(NAT10), an enzyme in the nucleus to inhibit the ac4C modification of HER2 mRNA, thereby promoting its degradation. However, in drug-resistant cells, XPO4 mediates the dissociation of circ-PPID from nuclear NAT10, leading to the retention of circ-PPID in the cytoplasm and the consequent loss of its inhibitory effect on HER2 [67] (Fig. 3).

ncRNA network mediated drug resistance

It is important to highlight that non-coding RNA networks exhibit a synergistic influence on the regulation of drug resistance [68].

Research conducted by Zhu et al. [69] demonstrated that UCA1 silencing suppresses YAP1 via miR-18a upregulation, thereby enhancing cell viability and trastuzumab sensitivity. Bie et al. [70] systematically characterized the negative regulatory relationship between HOTAIR expression levels and therapeutic response to trastuzumab, demonstrating that HOTAIR upregulation drives oncogenic phenotypes including enhanced proliferative capacity and metastatic potential. Mechanistic interrogation combining luciferase-based transcriptional profiling with immunoblot validation delineated a competing endogenous RNA circuitry mediated through miR-330 sequestration, forming the HOTAIR/miR-330/

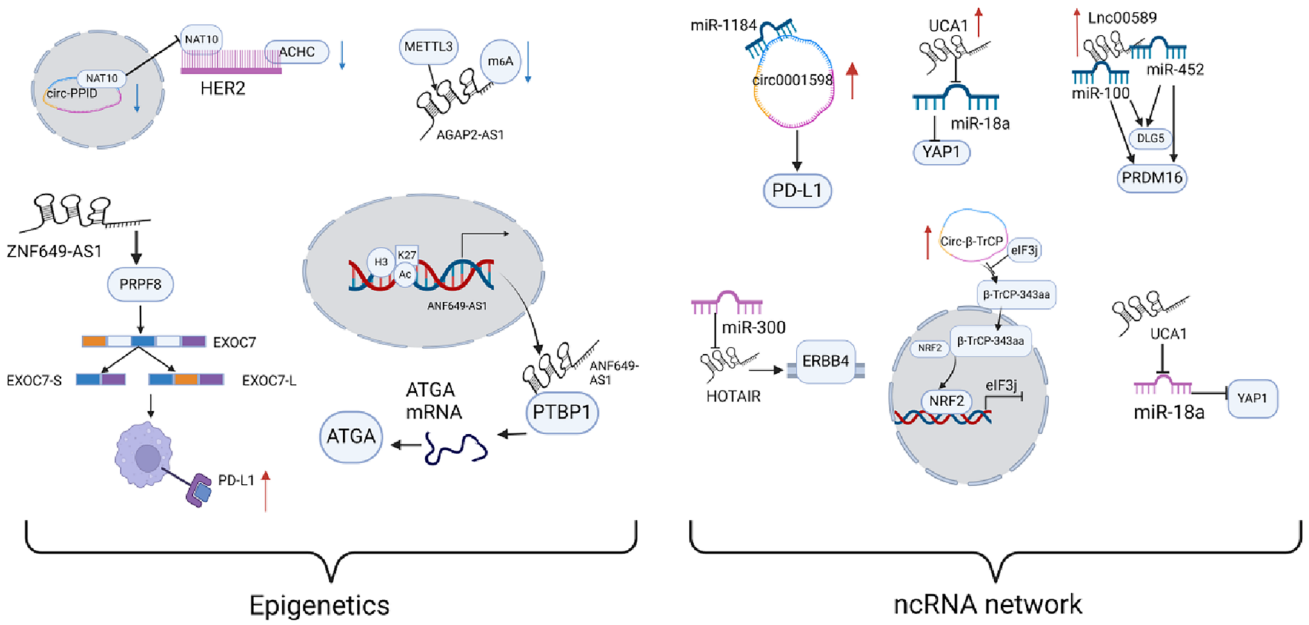

Fig. 3 ncRNA affects trastuzumab resistance through epigenetic crosstalk and ncRNA network

ERBB4 signaling axis. This molecular cascade fundamentally sustains drug-refractory phenotypes by rewiring HER family receptor signaling dynamics, providing novel mechanistic insights into trastuzumab resistance development [70]. Long non-coding RNAs typically sequester miRNAs to modulate the invasion and metastasis of HER2-positive tumors, thereby playing a role in trastuzumab resistance. LINC00589 has been shown to induce the simultaneous formation of sponge-like structures with miR-100 and miR-452, thereby inactivating their inhibitory effects on tumor suppressors such as DLG5 and PRDM16 [71]. This mechanism allows LINC00589 to exert multiple tumor-suppressive effects and counteract drug resistance. Furthermore, circular RNAs (circRNAs) can function as miRNA sponges, regulating gene expression and alternative splicing [72]. For instance, circ0001598 alleviates its inhibition of PD-L1 by binding to miR-1184, which promotes tumor evasion from CD8 T cell-mediated cytotoxicity and contributes to drug resistance. This finding suggests that targeting circ0001598 may enhance the efficacy of trastuzumab through improved immunotherapeutic strategies [73]. Additionally, circRNAs can interact with various proteins, modulating their activity and function [74]. Wang et al. [75] discovered the critical involvement of circular RNA circ-β-TrCP in mediating anti-HER2 therapeutic resistance. Functional characterization revealed that this circular transcript encodes a shortened polypeptide variant (β-TrCP-343aa) capable of antagonizing NRF2's binding capacity through molecular competition, thereby establishing novel post-transcriptional regulatory mechanisms underlying drug-refractory phenotype identified a circular RNA, circ-β-TrCP, that is closely associated with trastuzumab resistance. Under conditions of oxidative stress, NRF2 further inhibits eIF3j, establishing a positive feedback loop between β-TrCP-343aa and NRF2, which enhances the translational capacity of circ-β-TrCP and accelerates the development of drug resistance.

ncRNA applies new technology in the treatment effects of trastuzumab

High-throughput studies have elucidated the molecular network characteristics associated with trastuzumab resistance, highlighting the co-regulatory interactions between genes such as BIRC5 and E2F1, as well as non-coding RNAs like miR-574-3p [76]. Collectively, these findings underscore the multifaceted role of miRNAs in mediating trastuzumab resistance and highlight innovative strategies—such as nanotechnology-based delivery and extracellular vesicle (EV)-targeted approaches—for overcoming this clinical challenge. Aberrant expression of WIP1 and miR-21, located at chromosomal locus 17q23, is linked to breast cancer pathogenesis and the emergence of resistance to HER2-targeted therapies. Suppression of these molecules reduces proliferation, survival, and tumorigenic potential in HER2-positive breast cancer cells with 17q23 amplification. Targeted delivery of WIP1 and miR-21 inhibitors via pH-sensitive nanoparticles to HER2-positive tumors significantly inhibits tumor growth in preclinical models [77]. Extracellular vesicles (EVs), 40–160 nm membrane-bound particles derived from endosomal compartments, encapsulate diverse biomolecules

including proteins, DNA, and RNA [78]. Secreted by cancer cells, these vesicles mediate intercellular communication by transferring molecular cargo to distal cells. Increasing evidence highlights that EVs enriched in non-coding RNA (ncRNA) regulate drug resistance across multiple cancer types [79]. Exosomes vesicle lncRNA Linc00969 is overexpressed in trastuzumab-resistant BC patients. Linc00969 can upregulate HER2 expression at the protein level and maintain HER2 mRNA stability by binding to HUR. In addition, extracellular vesicle Linc00969 can regulate trastuzumab resistance by inducing autophagy [80]. In HER2-positive tumors, trastuzumab can upregulate PD-L1 through immune effector cells and the stimulation of IFN γ secretion, which can lead to drug resistance [81]. Liu et al. [82] reported in their latest research that circRNA nanoparticles (NCNP) coated with neutrophil membrane enhanced the immune response, promoted the recruitment of effector T cells, and to some extent reduced brain metastasis of HER2-positive breast cancer trastuzumab and immune resistance by delivering CXCL9 and anti-PD-1 antibodies. Yu et al. [83] demonstrated that OIP5-AS1, a long ncRNA, is upregulated in trastuzumab-resistant breast cancer cells. Functioning as a molecular sponge for miR-381-3p, OIP5-AS1 relieves repression of its target gene HMGB3. EV-mediated transfer of OIP5-AS1 activates the miR-381-3p/HMGB3 signaling axis, thereby enhancing trastuzumab resistance. Additionally, EV-derived OIP5-AS2 shows promise as a diagnostic biomarker for trastuzumab resistance. Further research reveals that EVs propagate trastuzumab resistance through intercellular transfer of miR-301aa-3p, suggesting this miRNA may serve as a non-invasive biomarker for monitoring resistance development [52]. Collectively, these findings not only underscore the critical role of miRNAs in mediating trastuzumab resistance but also introduce novel technological approaches to combat this clinical challenge.

ncRNA as a biomarker for trastuzumab resistance in HER2-positive tumors

Biomarkers serve as indicators of biological processes utilized to assess particular states or diseases. These markers are typically analyzed from bodily fluids or tissues through either invasive techniques, such as tissue biopsy, or non-invasive methods, such as fluid biopsy [84]. Biomarkers predominantly consist of proteins, including cytokines and receptors, as well as nucleic acids, particularly non-coding RNA(ncRNA) [85]. Cancer biomarkers are specific to certain cancer cell types and exhibit differential expression when compared to adjacent tissues, as well as dynamic changes throughout cancer progression and treatment [86]. Distinct ncRNA can be expressed variably across different tissues, cell types, and stages of tumors [87, 88]. Clinical biomarkers exhibit commendable specificity, sensitivity, and reproducibility, thereby serving a crucial function in tumor diagnosis, prognostic prediction, cancer recurrence monitoring, and assessment of responses to anti-cancer therapies [89]. Furthermore, these biomarkers can be evaluated in conjunction with other biomarkers to enhance diagnostic accuracy.

In the domain of forecasting treatment responses to trastuzumab in HER2-positive cancer, the significance of various non-coding RNA biomarkers is progressively being elucidated. Clinical investigations have demonstrated that miR-148a-3p possesses considerable predictive value in patients undergoing the HER2-positive MAGIC test, with its reduced expression being significantly associated with a 3-month progression-free response (PFR) (odds ratio = 0.11 [0.02–0.78], $P = 0.027$). However, no notable differences were identified in overall survival (OS) and progression-free survival (PFS) [90]. Zhang and colleagues conducted an analysis of 36 samples, revealing that the extracellular vesicles miR-1246 (AUC = 0.750) and miR-155 (AUC = 0.877) serve as effective biomarkers for distinguishing patients who exhibit resistance to trastuzumab, with miR-155 demonstrating a specificity of 97.2%. Furthermore, multivariate analysis established that these two microRNAs are independent predictors of event-free survival (EFS) in early-stage patients and progression-free survival (PFS) in those with metastatic disease [91]. Additionally, it is important to highlight that the expression profile of miR-125b possesses dual clinical relevance: Its expression is significantly elevated in gastric cancer tissues when compared to normal counterparts, with this overexpression strongly correlated with advanced clinical stages—including TNM classification—and adverse prognoses in HER2-positive patients ($P < 0.05$) [92].

Fundamental research has indicated that miR-21 may inhibit apoptosis in tumor cells, facilitate immune evasion by tumors, and enhance proliferation, thereby contributing to resistance against trastuzumab [93]. The relationship between the overexpression of miR-21 and resistance to trastuzumab remains a subject of debate within the clinical research community. A clinical study demonstrated that increased miR-21 expression in tumor biopsies from patients undergoing preoperative trastuzumab therapy correlates with attenuated treatment responsiveness [17]. A separate study involving 109 cases of primary breast tumors found that elevated levels of miR-21 were linked to larger tumor size, advanced tumor staging and grading, reduced patient survival, as well as HER2-positive and estrogen receptor-negative status [94]. Another finding indicates that elevated miR-21 expression does not reliably predict resistance to adjuvant trastuzumab treatment [95]. The discrepancies in findings may be attributed to the limited sample sizes in the studies (16 and 32 participants, respectively), variations in treatment regimens among patients (receiving trastuzumab every 3 weeks for 1 year

VS others underwent 3–4 cycles of taxotere, carboplatin, and herceptin), and differing standards for detection.

microRNAs, specifically miR-200c-3p and miR-210, have exhibited significant therapeutic potential in clinical settings. Variations in plasma concentrations of miR-200c-3p can serve as dynamic indicators of treatment efficacy; notably, its diminished expression levels correlate with FOXP3 overexpression, unfavorable prognoses, and reduced progression intervals [96]. Additionally, circulating miR-210 levels correlate with trastuzumab responsiveness, tumor presence, and lymph node metastasis. Significantly elevated preoperative miR-210 levels were observed compared to postoperative values ($P = 0.0297$), indicating a potential role in perioperative disease monitoring, and patients with lymph node metastasis displayed markedly higher levels than those without ($P = 0.030$) [97]. Before the start of neoadjuvant chemotherapy combined with trastuzumab, miR-210 expression in the residual disease cohort was significantly higher than in the complete remission (pCR) group ($P = 0.0359$) [97]. These findings suggest that plasma miR-210 could serve as a predictive and monitoring biomarker for responses to trastuzumab therapy. Within the landscape of long non-coding RNAs, PCA3 is established as a validated biomarker for prostate cancer [98]. Additionally, both H19 and ZNF649-AS1 have been identified as prognostic indicators in related oncological research. Patients with elevated H19 expression experienced significantly reduced progression-free survival (PFS) (HR = 2.34) and demonstrated a notable correlation with TNM staging [99]. Elevated ZNF649-AS1 expression was observed in trastuzumab-resistant patients, and Kaplan–Meier survival analysis indicated that high ZNF649-AS1 levels correlated with poor overall survival (OS) and progression-free survival (PFS) [62]. Circular RNA (circRNA) is characterized by its nuclease resistance due to its covalently closed circular structure, and its stable presence in extracellular vesicles positions it as a promising candidate for liquid biopsy markers [100]. Specifically, CircCDYL2 supports the HER2 signaling pathway by facilitating the formation of the GRB7-FAK complex, and its overexpression is significantly linked to decreased disease-free survival (DFS) and overall survival (OS) in patients ($P < 0.05$) [24].

These findings underscore the predictive and diagnostic potential of non-coding RNAs in addressing trastuzumab resistance. Molecules such as miR-148a-3p, the miR-1246/155 combination, miR-200c-3p, and H19/circCDYL2 exhibit promise for clinical application. Nonetheless, additional validation in larger patient cohorts remains essential, particularly for molecules with controversial roles such as miR-21. Furthermore, the development of standardized detection methodologies is critical to clarify their clinical significance.

Conclusion

This review systematically elucidates the significant regulatory mechanisms of non-coding RNA (ncRNA) in trastuzumab resistance in HER2-positive tumors. By reviewing the multidimensional molecular mechanisms through which miRNA, lncRNA, and circRNA affect drug resistance phenotypes, it was found that ncRNA can regulate signaling pathways. For example, targeting miR-21 can inhibit activation of the PI3K/AKT/mTOR pathway. circCDYL2 activates the HER2 signaling axis by stabilizing the GRB7 protein. ncRNA can also regulate the proliferation, apoptosis, and invasion phenotype of HER2-positive tumors to mediate HER2-positive tumor drug resistance. For example, miR-200c inhibits tumor stem cell characteristics by targeting CD44, and ZNF649-AS1 induces autophagy through the PTBP1-ATG5 axis. circ GN inhibits ferroptosis through SLC7A11. ncRNA can target TGF-β and affect tumor invasion, metastasis, and trastuzumab sensitivity [47]. In addition to the underlying molecular mechanisms, the ncRNA biomarkers such as exosomes miR-1246, miR-155, and lncRNA H19 are significantly associated with drug resistance and have potential clinical predictive value. It is worth noting that this article preliminarily integrates and systematically reveal the interaction of ncRNA in regulating trastuzumab resistance through epigenetic modifications (such as H3K27ac, m6A), exosome delivery of ncRNA, and ceRNA network. However, most mechanism studies are based on cell and animal models, so it may be unable to fully reproduce the complex tumor microenvironment and heterogeneity of human patients. And most clinical sample validation scales are small, such as only 23 cases in the miR-148a-3p cohort. Some results are controversial, such as the clinical relevance of miR-21, which may be related to sample heterogeneity and differences in detection methods. The expression of ncRNA is tissue-specific and dynamic, and existing detection techniques make it difficult to capture its spatiotemporal changes in the tumor microenvironment fully. The multi-target properties of ncRNA, such as miR-21 simultaneously regulating PTEN and immune escape, make functional analysis difficult, and there is insufficient research on cross-cancer universality. Existing ncRNA mimetics and antagonists have significant toxic side effects. For example, MRX34 is the first miRNA cancer treatment drug to enter phase I clinical trials. Due to severe immune-mediated toxicity and patient death, miRNA Therapeutics suspended the trial after 3 years [101]. Therefore, it is necessary to deepen further and expand the mechanism in the future: use single-cell sequencing and space transcriptome technology to analyze the heterogeneity of ncRNA in tumors combined with liquid biopsy,

achieve accurate and dynamic monitoring, and explore the regulatory role of ncRNA in other HER2-positive tumors such as gastric cancer and breast cancer. Establishing a multi-omics integration and treatment strategy is also essential, as well as combining epigenomic and proteomic data to construct an ncRNA resistance pathway network. It is also necessary to optimize the clinical research of ncRNA in HER2-positive tumor trastuzumab and carry out multi-center, extensive sample clinical cohort validation of key ncRNA markers such as miR-21, circCDYL2, H19. Clinical translation requires innovative drug delivery systems. Extracellular vesicles have better biocompatibility and biological distribution than synthetic delivery methods, but attention should be paid to optimizing the surface modification of extracellular vesicles to improve targeting. Lipid nanoparticles are the most commonly used delivery system, with high biocompatibility and low toxicity, which can enhance the affinity of oligonucleotides. Therefore, it is necessary to develop highly targeted exosomes and low-toxicity lipid nanoparticle carriers actively. Simultaneously, CRISPR/Cas9 technology should be combined to achieve precisely targeted knockout of resistance-related ncRNAs [102], efficiently achieving clinical translation. Clinical treatment can combine ncRNA therapy, such as miRNA mimetics and miRNA antagonists to reverse drug resistance. However, it is necessary to avoid the toxic side effects of these drugs, such as damage to the immune system and inflammatory reactions.

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Declarations

Conflicts of interest The authors declare no competing interests.

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