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Review

Non-coding RNAs in drug resistance of head and neck cancers: A review

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ABSTRACT

Head and neck cancer (HNC), which includes epithelial malignancies of the upper aerodigestive tract (oral cavity, oropharynx, pharynx, hypopharynx, larynx, and thyroid), are slowly but consistently increasing, while the overall survival rate remains unsatisfactory. Because of the multifunctional anatomical intricacies of the head and neck, disease progression and therapy-related side effects often severely affect the patient's appearance and self-image, as well as their ability to breathe, speak, and swallow. Patients with HNC require a multidisciplinary approach involving surgery, radiation therapy, and chemotherapeutics. Chemotherapy is an important part of the comprehensive treatment of tumors, especially advanced HNC, but drug resistance is the main cause of poor clinical efficacy. The most important determinant of this phenomenon is still largely unknown. Recent studies have shown that non-coding RNAs have a crucial role in HNC drug resistance. In addition, they can serve as biomarkers in the diagnosis, treatment, and prognosis of HNCs. In this review, we summarize the relationship between non-coding RNAs and drug resistance of HNC, and discuss their potential clinical application in overcoming HNC chemoresistance.

1. Background

Head and neck cancer (HNC) is a major global health problem. More than 890,000 new cases of HNC and approximately 450,000 HNC-related deaths occur every year [1,2]. The majority of cases are HN squamous cell carcinoma (HNSCC) [3], involving the stratified epithelium of the oral cavity, pharynx, and larynx, with an overall 5-year survival rate of only 40%–50% [3]. Most HNC is closely related to tobacco and alcohol use [1–3]. Patients with HNC might have symptoms including hoarseness, dysphagia, pain, neck mass, and ulcers, which require a multidisciplinary approach involving surgery, radiation therapy, and chemotherapy [4]. Although the treatment is effective for early and locally advanced disease, the prognosis of recurrent and metastatic disease remains poor [5]. Clinically, more than 65% of patients are diagnosed with advanced disease because of the lack of early diagnosis [6]. However, both radiotherapy and surgery reduce patients'

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quality of life at this stage [2]. Radiotherapy usually produces obvious side effects, while surgery can significantly affect the normal physiological structure and function of patients [2,7]. Additionally, targeted therapy for HNC has been incorporated into clinical treatment guidelines, but its clinical response and long-term effect are limited, and high costs are associated with this treatment [8].

In recent years, chemical treatment of advanced HNC has been increasingly recognized [9]. In early phase II clinical trials in patients with advanced HNSCC, significant single-agent response rates were up to 30% [5,10]. To date, cisplatin (CDDP) and paclitaxel (PTX) based chemotherapy and adjuvant radiotherapy is still the first-line treatment for advanced HNC patients. Unfortunately, patients do not respond well to chemotherapy and even develop resistance to chemotherapy, which leads to disappointing clinical results and is a major cause of death [11,12]. Resent data have shown that approximately 55% of HNC patients deteriorate due to the above reasons [2,3,13]. Currently, the mechanisms for HNC drug resistance are linked to drug efflux changes, cell apoptosis, DNA damage repair, drug target mutations, epithelial-mesenchymal transformation (EMT), and cancer stem cells (CSCs) [14–17].

Disappointingly, the most important determinant of this phenomenon is still largely unknown. With progress in bioinformatics analysis and next-generation sequencing, 98% of human DNA has been identified as non-protein coding [18]. Non-coding RNAs are a large class of RNA transcripts without protein coding potential. Recent studies have shown that non-coding RNAs act as underlying factors in cellular proliferation, migration, apoptosis, angiogenesis, immune response, and autophagy [19,20]. They are also closely related to the most common diseases, especially cancer [21,22]. Moreover, non-coding RNAs are involved in drug resistance in multiple types of cancer including HNC [23,24]. Therefore, a better understanding of the mechanisms of non-coding RNAs and chemoresistance is important for treating HNC.

Most non-coding RNAs involved in chemoresistance are microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs) [25,26]. MiRNAs are a type of single-stranded RNA molecule that was first discovered in 1993 in the *Caenorhabditis elegans* lin-4 locus with a length of 18–22 nt [27]. It is believed that miRNAs mainly match with a target 3′-UTR to play a regulatory role, leading to mRNA degradation or translation inhibition (Fig. 1a) [28]. The most commonly used definition of long non-coding RNA is based on the threshold of 200 nt of RNA length that lacks a meaningful open reading frame [29]. Functionally, lncRNAs are classified as signaling, decoy, guide, and scaffold lncRNAs (Fig. 1b) [29]. Unlike linear RNAs, circRNAs have a special circular covalent bonding structure that renders them more tolerant to nucleic exonucleases [30]. CircRNAs are mainly divided into exonic circRNAs, intron circRNAs, and exon–intron circRNAs (Fig. 1c) [31–34]. Functionally, circRNAs act as miRNA sponges, interact with RNA binding proteins, translate proteins, and regulate transcription or splicing and epigenetic alterations (Fig. 1c) [22].

In this review, we summarize the relationship between non-coding RNAs and drug resistance of HNC.

2. Current known mechanisms of HNC drug resistance

2.1. Drug efflux

ATP-binding cassette (ABC) is a class of transmembrane transporters and includes P-glycoproteins (P-gp), breast cancer resistance protein (BCRP), and multi-drug resistant-related protein 1 (MRP1) [14]. ABC can actively transport intracellular drugs across the membrane in a reverse concentration gradient, pump chemotherapeutic drugs out of tumor cells, and reduce intracellular drug accumulation, which results in HNC drug resistance [35]. The expression of transcription factors Twist1 and P-gp/MDR1 in PTX-induced HNC resistant cells was significantly higher than that in primary cells, and Twist1 could directly regulate the expression of P-gp [36].

2.2. Inhibition of cell apoptosis

In drug-resistant cancer cells, the apoptotic pathway is often dysfunctional. Survivin is a member of the apoptosis inhibitory protein family and activates the PI3K/AKT signaling pathway during CDDP treatment [37]. It also has a critical role in promoting PTX resistance in HNSCC cells by inhibiting apoptosis [38].

2.3. DNA damage repair

CDDP is commonly used in HNC clinical treatment. Its main mechanism of action, to kill tumor cells is to destroy DNA and then cause promote cell apoptosis [39]. Therefore, the enhanced ability of tumor cells to repair damaged DNA will naturally be accompanied by the resistance of chemotherapeutic drugs. As a single-stranded DNA endonuclease, the mRNA and protein expression of ERCC1 is increased in HNSCC cells treated with CDDP, which results in the enhancement of cell chemoresistance [40].

2.4. Drug target mutations

Mutations of target genes that result in changes in their expression levels is one of the mechanisms of chemotherapy resistance of tumor cells [14]. Epidermal growth factor receptor (EGFR) is a type of tyrosine kinase receptor that is expressed in 90% of HNSCC, and upregulation of EGFR expression is closely related to prognosis [41]. Alternative activation of other tyrosine kinase receptors such as RET in HNSCC leads to EGFR TKI drug resistance [42].

2.5. EMT and CSCs

In the process of EMT, the phenotype of epithelial cells changes from a pebble-like phenotype to a fibroblast phenotype, and is accompanied by increased activity and invasiveness, which has been shown to be related to HNSCC drug resistance [43,44]. CSCs are a subpopulation of tumor-causing cells that undergo self-renewal, enabling them to quickly adapt to changes in the surrounding environment, and thus they are more resistant to chemotherapy than other tumor cells [43]. CD133 + CD44 + CSCS isolated from laryngeal squamous cell carcinoma (LSCC) are more resistant to chemotherapy and are expected to be a new target for LSCC treatment [45].

3. MiRNAs in HNC cell drug resistance

Studies conducted in the past few years have shown that 30% of the genes that encode proteins in humans are regulated by miRNAs [46]. miRNAs may be relevant to cancer chemosensitivity and chemoresistance including HNC (Table 1); the molecular mechanisms are shown in Fig. 2 [47].

3.1. MiRNAs mediate drug resistance of oral cancer

There were more than 350,000 new cases of oral cancer annually worldwide [1], most of which are oral squamous cell carcinoma (OSCC) [48], with resistance to CDDP being the main reason for its poor 5-year survival [49]. Tongue squamous cell carcinoma (TSCC) is common [50]. Recent studies have shown that miRNAs are involved in the drug resistance of oral cancer. Chang et al., in comparing normal human oral keratinocytes, discovered decreased expression of *let-7d* and increased expression of Twist and Snail in OSCC cancer cell lines and primary cultures. Furthermore, overexpression of *let-7d* significantly inhibited CDDP- and 5-fluorouracil (5-FU)-resistant abilities of OSCC cells [51]. *Let-7d* also regulates multidrug resistant (MDR) genes in ovarian cancer (OVC) [52] and is downregulated in breast cancer (BRC) [53], meningioma [54], gastric cancer (GC) [55], kidney cancer [56], and pancreatic cancer (PAC) [57].

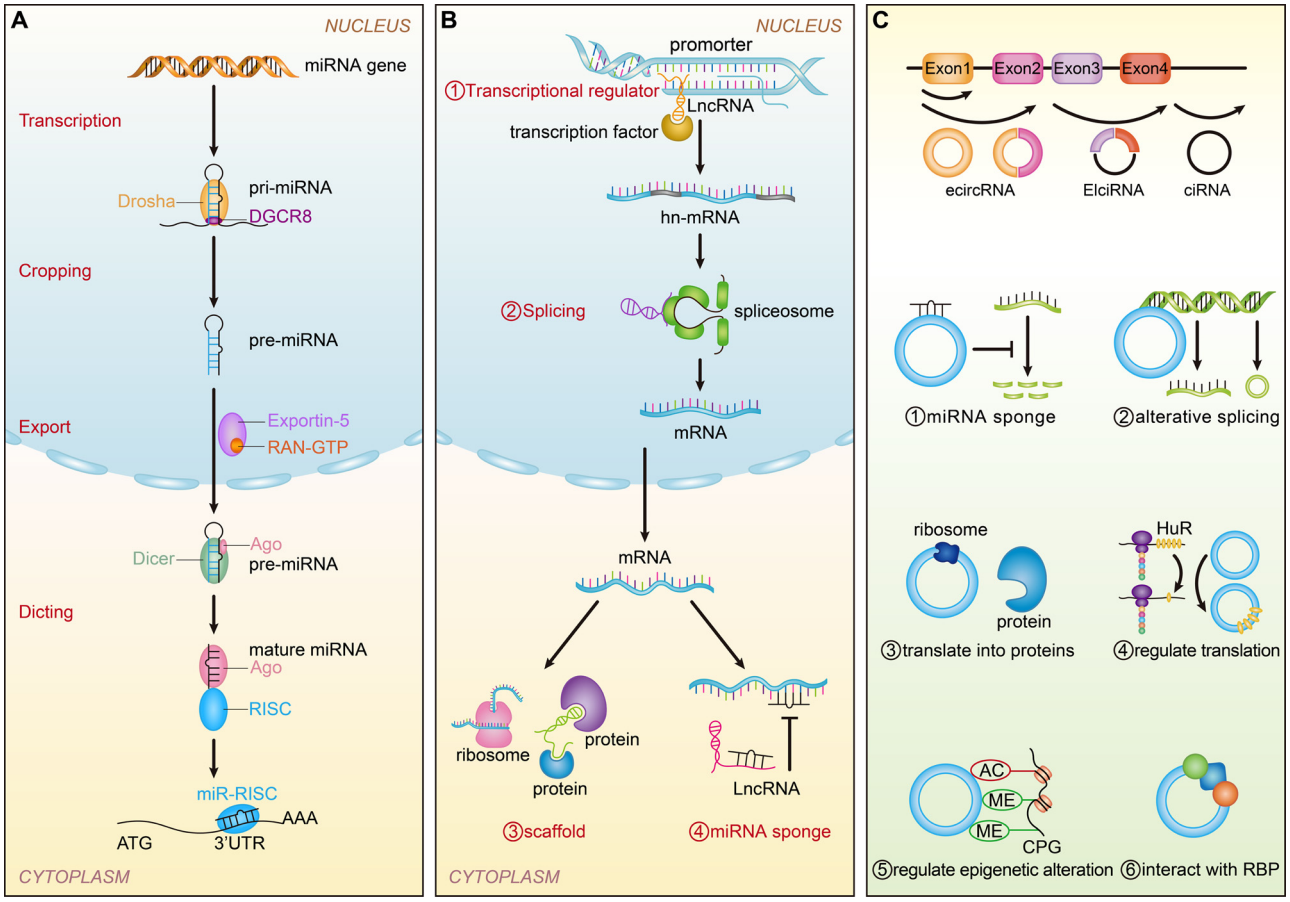

Fig. 1. Schematic of the generation, processing, and biological function of non-coding RNAs. a. microRNAs; b. lncRNAs; c. circRNAs.

MiRNAs also affect signaling pathways to regulate the resistance of OSCC. *MiR-365-3p* regulates 5-FU resistance by inhibiting EHF/KRT16/β5-integrin/c-Met signaling, thereby improving treatment efficacy in OSCC [58]. *MiR-654-5p* promotes CDDP and 5-FU resistance of OSCC via GRAP-mediated RAS/MAPK signaling [59]. It also attenuates disease progression in BRC [60], Hodgkin lymphoma [61], GC [62], and prostate cancer (PRC) [63]. In tongue cancer, miRNAs can mediate drug resistance by regulating signaling pathways. Deregulation of *miR-24* was found to be associated with tumor progression, cell survival, and CDDP resistance by regulating the PTEN/AKT pathway in TSCC [64]. Furthermore, *MiR-24* can hamper chemotherapy-induced apoptosis in BRC [65], while *miR-23a* promotes CDDP resistance by modulating Twist expression in TSCC cells [66], and also inhibits the effect of CDDP via the PTEN/PI3K/AKT pathway in lung cancer (LCA) cells [67], decreases 5-FU sensitivity in colorectal carcinoma cells by directly targeting ABCF1 [68], and significantly potentiates the gefitinib effect in human hepatocellular carcinoma (HCC) [69].

However, most miRNAs regulate drug resistance by decreasing the expression of target genes in TSCC. *MiR-181a* directly targets Twist1, and its overexpression leads to a reversal of CDDP resistance in TSCC cells [70]. Recently, it was found to be related to drug resistance in PRC [71], LCA [72], GC [73], BRC [74], and glioma [75]. Overexpression of *miR-200b* and *miR-15b* effectively increases the efficacy of CDDP [76]. Furthermore, *miR-15b* increases the sensitivity of CDDP by targeting TRIM14 in TSCC [77]. Also, overexpression of *miR-200b* increases doxorubicin (DOX) sensitivity in BRC [78], CDDP sensitivity in OVC [79], and docetaxel sensitivity in PRC [80], and could promote MDR in small cell lung cancer [81]. Similarly, *miR-15* was found to be related to gemcitabine (GEM) resistance of PAC [82], CDDP resistance of lung adenocarcinoma (LAC) cells [83], 5-FU resistance of colon cancer [84], and MDR of GC [85] and osteosarcoma [86]. *MiR-222* directly targets *ABCG2* and decreases its expression in TSCC, while its overexpression reduced CDDP resistance in TSCC [87]. It mediates some signaling pathways to modulate drug resistance in BRC [88], bladder cancer (BLC) [89], and colorectal cancer (CRC) [90].

In tongue cancer cells, suppression of *miR-21* could promote the chemosensitivity of TSCC cells to CDDP by targeting *PDCD4* [91] and decrease the sensitivity of CDDP via targeting *CADM1* [92]. *MiR-21* in exosomes from CDDP-resistant OSCC cells confirmed that it induces CDDP resistance by regulating the expression of *PTEN* and *PDCD4* [93]. Moreover, it contributes to the drug resistance of other kinds of cancers such as GEM resistance in PAC [94], CDDP resistance in GC cells [95], sorafenib resistance in HCC cells [96], 5-FU resistance in PAC [97], and MDR in renal carcinoma [98].

3.2. MiRNAs mediate drug resistance of nasopharyngeal carcinoma (NPC)

Despite progress in the diagnosis and treatment of NPC over the past few years, some patients still have advanced disease accompanied by tumor metastasis, and patients with high-stage disease are not sensitive to chemotherapy [99], which leads to recurrence [100]. Therefore, clarifying the mechanism of drug resistance and identifying new chemotherapy methods for NPC are needed. In recent years, miRNAs have been widely reported to be involved in NPC resistance.

MiR-21 is related to oral cancer drug resistance and is also reported in NPC. Exogenous LMP1 can increase *miR-21* expression, leading to CDDP resistance of NPC [101]. *MiR-634* was downregulated in PTX resistant CNE-1 cells; restoration of its expression re-sensitized CNE1 cells to PTX in vitro [102]. It also regulates drug sensitivity in OVC [103] and glioma [104]. *MiR-132* is poorly expressed in CDDP-resistant CNE2 cells, and its overexpression of restored the CDDP treatment response in NPC cells by regulating *FOXA1* [105]. *MiR-132* also promoted

Table 1
HNCs cell drug resistance related miRNAs.

Tumor type	miRNA	Cell line	Chromosomal location	Expression level	Target genes	Functions	Corresponding drugs	Refs
OSCC	let-7d	OECM1, primary cell	9:96,941,116-96,941,202	down	Twist, Snail	decrease the expression of Twist, Snail	CDDP,5-FU	[51]
OSCC	miR-365-3p	OC3, CGHNC9	/	up	EHF	enhancing β5-integrin/c-met signaling pathway	5-FU	[58]
OSCC	miR-654-5p	Tca8113, CAL27	14:101506571-101506592	up	GRAP	through Ras/MAPK signaling pathway	CDDP,5-FU	[59]
TSCC	miR-24	TSCC cell line, CDDP-resistant cell line	X:151127050-151127130	up	PTEN	negatively regulates PTEN/Akt pathway	CDDP	[64]
TSCC	miR-23a	SCC-4, Tca8113	19:13947401-13947473	up	Twist	inducing Twist expression by a JNK-dependent mechanism	CDDP	[66]
TSCC	miR-181a	CAL27, SCC-15	(miR-181a-1) 1:198828173-198828282 (miR-181a-2) 9:127454721-127454830	down	Twist1	decrease the expression of Twist1	CDDP	[70]
Tongue cancer	miR-200b, miR-15b	CAL27, SCC-25	(miR-200b) 1: 1167104-1167198 (miR-15b) 3:160404588-160404685	down	BMI1	reverse the phenotype of EMT	CDDP	[76]
TSCC	miR-15b	SCC-25	3:160404588-160404685	down	TRIM14	decrease the expression of TRIM14	CDDP	[77]
TSCC	miR-222	CAL27	X:45606421-45606530	down	ABCG2	decrease the expression of ABCG2	CDDP	[87]
TSCC	miR-21	Tca8113, CAL27	17:57918672-57918692	up	PDCD4	decrease the expression of PDCD4	CDDP	[91]
Tongue cancer	miR-21	Tca8113, SCC-25, CAL27	17:57918672-57918692	up	CADM1	decrease the expression of CADM1	CDDP	[92]
OSCC	miR-21	HSC, SCC-9	17:57918672-57918692	up	PTEN, PDCD4	decrease the expression of PTEN and PDCD4	CDDP	[93]
NPC	miR-21	CNE2, HONE1	17:57918672-57918692	up	PDCD4, Fas-L	decreases the expression of PDCD4 and Fas-L	CDDP	[101]
NPC	miR-634	CNE1	17:64783190-64783286	down	/	miR-634 sensitizes NPC cells to PTX	PTX	[102]
NPC	miR-132	CNE2	17:1953202-1953302	down	FOXA1	decrease the expression of FOXA1	CDDP	[105]
NPC	miR-125b	CNE2	(miR-125b-1) 11:121970465-121970552 (miR-125b-2) 21:17962557-17962645	down	Bcl-2	decrease the expression of Bcl-2	CDDP	[110]
NPC	miR-26b	CNE2, HNE1	2:219267369-219267445	down	JAG1	decrease the expression of JAG1	CDDP	[115]
LSCC	miR-26b	HEp-2	2:219267369-219267445	down	ATF2	decrease the expression of ATF2	CDDP	[124]
LSCC	miR-125a	HEp-2	19:52,196,559-52,196,580	down	HAX-1	decrease the expression of HAX-1	CDDP	[122]
LSCC	miR-133a	HEp-2	(miR-133a-1) 18:19405659-19405746 (miR-133a-2) 20:61162119-61162220	down	ATP7B	decrease the expression of ATP7B	CDDP	[123]
PTC	miR-206	Nthy-ori3-1, TPC-1	2:219267369-219267445	down	MAP4K3	decrease the expression of MAP4K3	Euthyrox	[133]
ATC	miR-27b-3p	SW1736,8305C	9:97847727-97847823	up	PPARγ	decrease the expression of PPARγ	DOX	[134]
HNC	let-7a	primary HNC cells	let-7a-1(9: 94,175,957-94,176,036) let-7a-2(11: 122,146,522-122,146,593) let-7a-3(22: 46,112,749-46,112,822)	down	/	via stem-like properties ablation	CDDP	[140]
HNSCC	miR-24-3p	SCC-15	/	up	CHD5	decrease the expression of CHD5	5-FU, OXA	[147]
HNC	miR-196a	SCC-4, SCC-9, SCC-25, CAL27	12:54385583-54385604	up	CDKN1B, ING5	decrease the expression of CDKN1B, ING5	CDDP	[150]

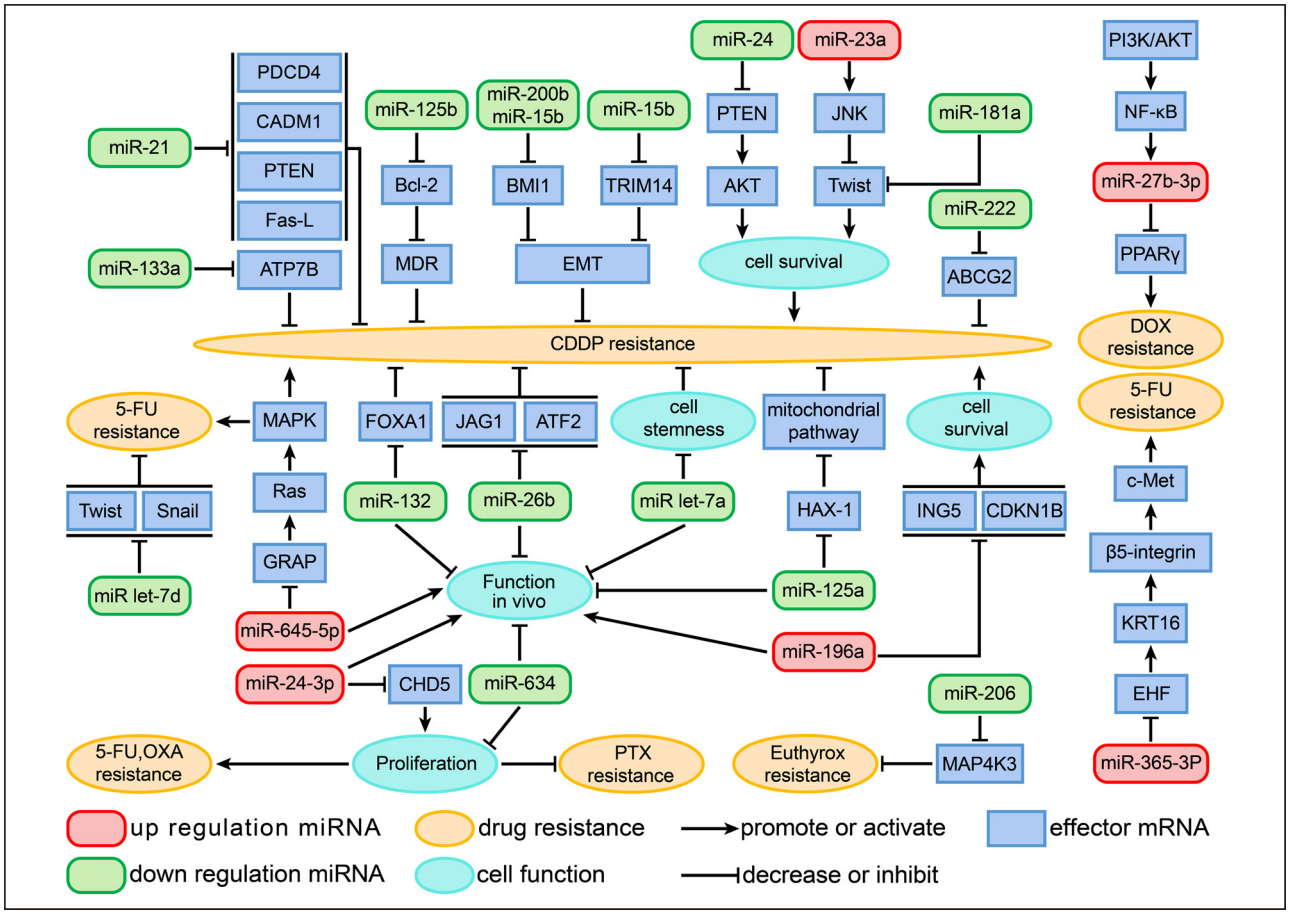

Fig. 2. Overview of the molecular mechanisms of miRNAs in HNC drug resistance.

CDDP-resistance in Lgr5+ GC cells [106]; it regulated DOX sensitivity in CRC cells by modulating ERK1 expression [107] and induced temozolomide resistance by targeting *TUSC3* in GEM [108]. *MiR-132* and *miR-212* regulate DOX resistance in BRC by inhibiting PTEN/AKT/NF-κB signaling [109]. *MiR-125b* modulates the CDDP resistance of NPC cells, which may represent a novel therapeutic target of MDR in NPC [110], and is involved in cancer drug resistance in OVC [111], gallbladder cancer [112], and BRC [113]. Importantly, it regulates 5-FU resistance by increasing autophagy in CRC [114]. Using CDDP-resistant cells, decreased *miR-26b* expression led to CDDP resistance in NPC [115]. *MiR-26b* also decreased temozolomide resistance in glioma cells [116], inhibited PTX resistance by silencing *CDC6* in GC [117], regulated non-small cell lung cancer (NSCLC) cell chemosensitivity by modulating *PTEN* [118], and enhanced DOX sensitivity in HCC [119].

3.3. MiRNAs mediate drug resistance of laryngeal carcinoma

Laryngeal cancer accounts for approximately 20% of HNC [1], the drug resistance of which has affected the survival rate of patients [120]. In the past few years, many drug resistance mechanisms have been found in LSCC [121], including the expression of miRNA regulatory genes [122–124]. Downregulated expression of *miR-26b* increased CDDP resistance by targeting *ATF2* in LSCC [124]. *MiR-125a* promotes CDDP-induced apoptosis in LSCC, and its overexpression improved MDR to vincristine, etoposide, and DOX [122]. It also contributed to the emergence of BRAF inhibitor resistance [125], regulated GEM resistance in PAC [126], and activated CSCs in colon cancer [127]. *MiR-133a* is weakly expressed in LSCC cells and enhances the sensitivity of CDDP by decreasing the expression of *ATP7B* [123]. It is also associated with 5-FU and CDDP resistance in HCC [128] and DOX resistance in BRC [129].

3.4. MiRNAs mediate drug resistance of thyroid cancer

Thyroid carcinoma (TC) is an endocrine tumor of HNC. In 2018, there were more than 550,000 new cases worldwide, and its incidence ranks highest among HNC [1]. Generally, after reasonable treatment, patients with TC have good prognosis [130], but there are still some with relapse that require drug treatment, and the occurrence of drug resistance will still cause mortality risk to patients [131]. The mechanism of drug resistance in TC is not clear [132], but some researchers reported that miRNAs are involved [133,134]. *MiR-27b-3p* decreased DOX sensitivity of anaplastic thyroid cancer cells (ATCs) [134]. It also potentially reversed MDR by targeting *CBLB/GRB2* in BRC [135] and enhanced the sensitivity of tamoxifen by downregulating *NR5A2* and *CREB1* expression [136]. *MiR-206* was significantly downregulated in papillary thyroid carcinoma (PTC), and its overexpression decreased the expression of *MAP4K3* and inhibited levothyroxine resistance [133]. Furthermore, it suppressed CDDP resistance by targeting MAPK2 signaling [137], and modified 5-FU sensitivity in colon cancer cells [138] and CDDP resistance in human LAC cells [139].

3.5. MiRNAs mediate drug resistance of HNC

Some miRNAs are involved in the drug resistance of HNCs. Overexpression of *let-7a* eliminated self-renewal and CDDP resistance in HNC-ALDH1+ cells [140]. Over the past few years, *let-7a* was confirmed to play important role in GEM resistance of PAC [141], epirubicin resistance in BRC [142], DOX resistance in PRC [143], PTX

resistance in BRC [144], and cetuximab resistance in HCC [145]. Moreover, *let-7a* could be a novel marker for drug resistance in GC [146]. *MiR-24-3p* was found to be highly expressed in HNSCC; it regulates 5-FU and oxaliplatin (OXA) resistance of HNSCC cells by modulating *CHD5* expression [147]. Furthermore its expression leads to VP16-DDP resistance in small cell lung cancer cells via targeting of *ATG4A* [148] and to OVC cell chemoresistance to CDDP [149]. A high level of exosomal *miR-196a* derived from CAFs (cancer-associated fibroblasts) was found related to poor overall survival and conferred CDDP resistance in HNC by regulating the expression of *CDKN1B* and *ING5* [150]. *MiR-196a* could decrease CDDP sensitivity in A549/DDP NSCC [151] and drug resistance in chronic myeloid leukemia stem cells [152].

Thus, miRNAs mainly affect the drug resistance of HNC by affecting the expression of their target mRNAs, and by regulating apoptosis signal pathways, EMT and CSCs. This is also consistent with the function of miRNAs and provides new insights for the better understanding of the drug treatment and resistance of HNC.

4. Long non-coding RNAs in HNC cell drug resistance

LncRNAs regulate almost every cellular process and are widely recognized as critical regulators of tumors and tumorigenesis and as a potentially important mediator of drug resistance by regulating apoptosis, drug efflux systems, drug metabolism, DNA repair, EMT, and autophagy [17,153–155]. *BCAR4* induced resistance to hydroxytamoxifen following its ectopic expression in zr-75-1 cells [156]. Moreover, lncRNAs are widely involved in HNC cell chemotherapy resistance (Table 2), the molecular mechanisms of which are shown in Fig. 3.

4.1. CDDP resistance

In 1978, CDDP was approved by the US Food and Drug Administration for the clinical treatment of various solid tumors including HNC [157,158]. The main mechanism of CDDP is inhibition DNA replication and RNA transcription to halt cells in G phase and promote their apoptosis [39]. However, the high incidence of CDDP resistance limits its clinical application, including in HNC. Over the past few years, many studies have shown that lncRNAs are involved in CDDP resistance in HNC. These studies provide new ideas for CDDP resistance research in HNC and will be realized to improve the therapeutic effect of CDDP in the future.

Overexpression of lncRNA *CILA1* reduces the CDDP sensitivity of chemoresistant cells and regulated EMT in TSCC cells via the Wnt/β-catenin pathway [159]. The lncRNA *UCA1* is overexpressed in TSCC tissues; its knockdown markedly increases CDDP-induced apoptosis and chemosensitivity. The difference is likely due to *UCA1* inhibition of CDDP-activated PI3K/AKT signaling [160]. Similarly, *UCA1* is upregulated in OSCC, increasing CDDP chemoresistance and restraining apoptosis by suppressing *miR-184* expression in OSCC cells [161]. Moreover, *UCA1* enhances CDDP resistance in BLC [162] and OVC [163], increases 5-FU resistance in CRC [164] and GC [165], and induces tamoxifen resistance in BRC [166] and docetaxel resistance in PRC cells likely via the *UCA1/miR-204/*SIRT1 axis [167]. *UCA1* contributes to NSCLC cell acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway and EMT [168]. It even emerges as a competitive endogenous RNA of *MDR1* that induces imatinib resistance via sequestering *miR-16* in chronic myeloid leukemia cells [169]. HOX transcript antisense RNA (*HOTAIR*) was first reported to regulate transcription in 2007 [170]. *HOTAIR* was found to be overexpressed and to decrease the CDDP sensitivity of OSCC cells as an oncogene [171]. *HOTAIR* also enhances CDDP resistance by decreasing the expression of *EZH2* in LSCC AMC-HN-8 cells [172].

Similarly, *HOTAIR* is involved in CDDP resistance of pulmonary adenocarcinoma [173], DOX resistance of BLC cells [174], and tamoxifen resistance of BRC [175]. *LINC-PINT* expression is significantly reduced in tumor tissues, and it increases the CDDP resistance of LSCC via the *miR-425-5p/PTCH1/*SHH axis [176]. In addition, the expression of *LINC-PINT* is decreased in other cancer tissues such as PAC [177], GC [178], osteosarcoma [179], glioblastoma [180], and CRC [181]. It also serves as a biomarker of diagnosis and prognosis for human PAC [177]. Using human LSCC specimens and paired adjacent normal tissues from 24 patients, the lncRNA *AFAP1-AS1* was found to increase CDDP resistance by controlling *miR-320a* activity and regulating *RBPJ* expression [182]. *AFAP1-AS1* is overexpressed in esophageal cancer [183], pancreatic ductal adenocarcinoma [184], LCA [185], HCC [186], OVC [187], CRC [188], biliary tract cancers [189–191], and GC [192]. Overexpression of *AFAP1-AS1* is related to tumor size and metastasis, and may be used as a drug efficacy biomarker in cancer patients [183–192].

In NPC tumor tissues, downregulation of lncRNA *ROR* in CNE2 cells enhanced the sensitivity of CDDP by activating the p53 pathway [193]. *ROR* regulates *miR-205* expression by changing tamoxifen resistance in BRC [194] and modulates the *miR-124/PTBP1/*PKM2 axis to alter GEM resistance in PAC [195]. *ROR* is also related to CDDP resistance in NSCLC by activating PI3K/AKT/mTOR signaling [196] and docetaxel chemoresistance of LAC by the EMT pathway [197]. The expression of lncRNA *NEAT1* is high in NPC tissues, which enhances CDDP resistance of NPC cells by inhibiting *let-7a-5p* expression and activating the RAS-MAPK pathway [198]. *NEAT1* contributes to DOX resistance in GC [199] and BLC [200], CDDP [201] and PTX [202] resistance in NSCLC, sorafenib resistance in HCC [203], and chemoresistance in BRC [204]. Moreover, data from The Cancer Genome Atlas database showed that different levels of *NEAT1* are significantly related to survival in HNC (Fig. 4e).

Table 2
HNCs cell drug resistance related lncRNAs.

Tumor type	lncRNA	Cell line	Chromosomal location	Expression level	Target genes	Functions	Corresponding drugs	Refs
TSCC	CILA1	CAL27, SCC-9	/	up	/	activating Wnt/ β-catenin pathway	CDDP	[159]
TSCC	UCA1	CAL27, SCC-9	19: 15,828,206-15,836,326	up	/	activating PI3K/Akt signaling pathway	CDDP	[160]
OSCC	UCA1	Tca8113	19: 15,828,206-15,836,326	up	SF1	ceRNA	CDDP	[161]
OSCC	HOTAIR	KB, CAL-27	12: 53,962,308-53,974,956	up	/	decreases the CDDP sensitivity	CDDP	[171]
LSCC	HOTAIR	AMC-HN-8	12: 53,962,308-53,974,956	up	EZH2	decrease the expression of E2H2	CDDP	[172]
LSCC	PINT	HEp-2	7: 130,938,963-131,110,176	down	PTCH1	inhibiting miR-425-5p/PTCH1 axis	CDDP	[176]
LSCC	AFAP1-AS1	HEp-2	4: 7,754,090-7,778,928	up	RBPJ	ceRNA	CDDP	[182]
NPC	ROR	CNE2	18: 57,054,558-57,072,119	up	/	inhibit p53 pathways	CDDP	[193]
NPC	NEAT1	CNE1, CNE2	11: 65,422,774-65,445,540	up	Rsf-1	activating Ras-MAPK pathway	CDDP	[198]
ATC	PTCSC3	FTC 238	14: 36,136,108-36,176,468	down	INO80	inhibiting STAT3/INO80 axis	DOX	[205]
NPC	CCAT1	CNE1, CNE2	8:128,219,629-128,231,333	up	CPEB2	ceRNA	PTX	[206]

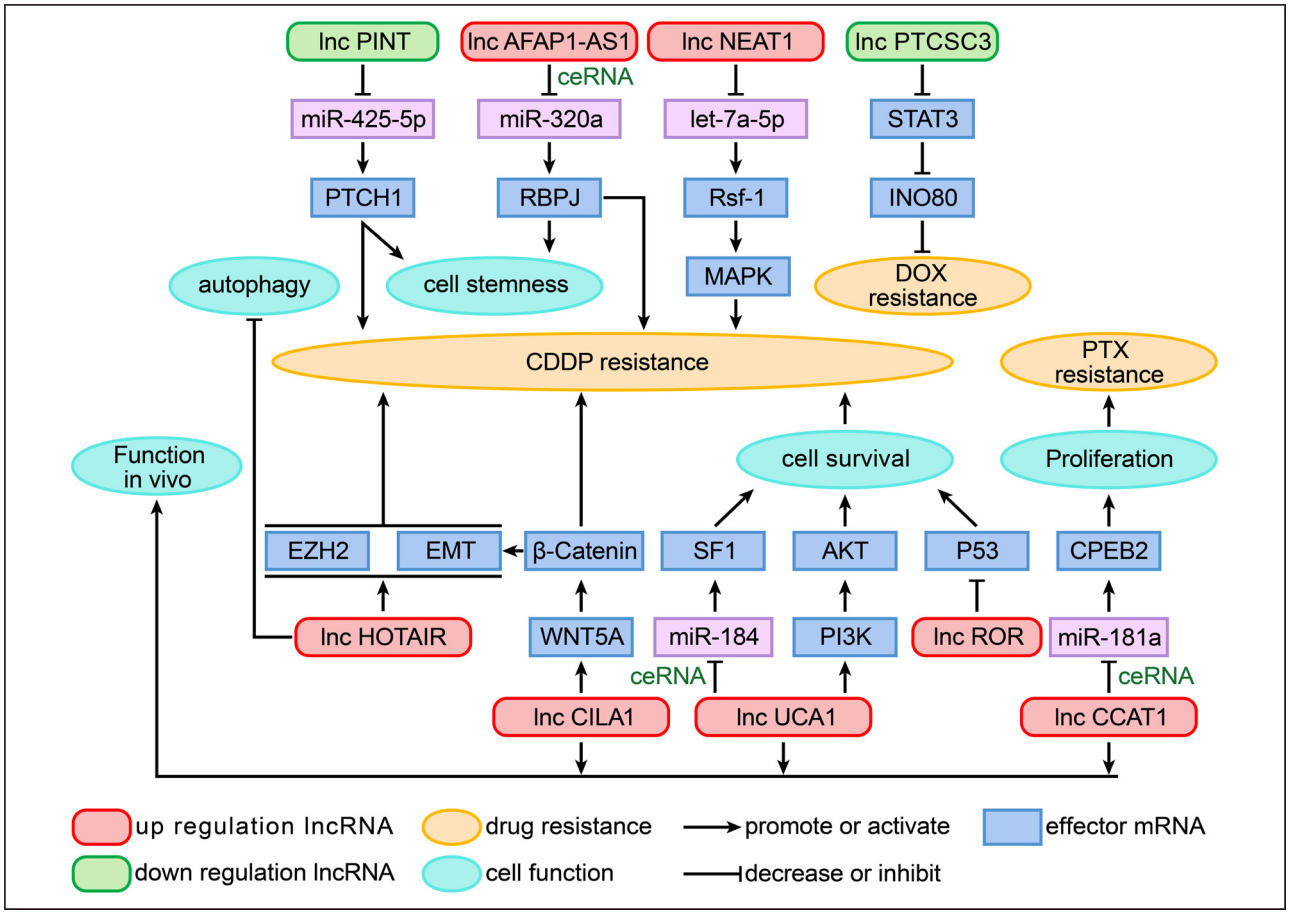

Fig. 3. Overview of the molecular mechanisms of lncRNAs in HNC drug resistance.

4.2. Other drug resistance

PTCSC3 is expressed at low levels in anaplastic ATC tissues, and overexpression of *PTCSC3* inhibits the expression of *STAT3* and *INO80* and enhances the docetaxel sensitivity of ATCs [205]. Another study showed that the lncRNA *CCAT1* can enhance the level of CPEB2 protein and inhibit CDDP sensitivity in NPC cells by acting as a competing endogenous RNA to sponge *miR-181a* [206]. Furthermore, *CCAT1* promoted DOX resistance in LAC [207] and reduced CDDP sensitivity in NSCC cells via the *CCAT1/miR-130a-3p/SOX4* axis [208].

Despite some studies of lncRNA regulation of drug resistance in HNC, further exploration is needed to explain its potential mechanism. Further in-depth study of the mechanisms of chemoresistance induced by lncRNAs in HNC should be conducted to identify potential biomarkers of cancer diagnosis and provide valuable methods for transformation therapy.

5. CircRNAs in HNC cell drug resistance

CircRNAs were first identified around 42 years ago in RNA viruses [209]. Because of their low expression, circRNAs were once considered a byproduct of RNA missplicing or splicing until they could be placed in the eukaryotic tree [210]. Recently, numerous studies have shown that circRNAs have important roles in cancer development, metastasis, and stemness [34,211,212]. They are also are involved in tumorigenesis, progression, and invasion, and can serve as diagnostic and prognostic biomarkers of HNC [213]. In the past few years, circRNAs have been found to be involved in tumor drug resistance. The circRNA *MTO1* promoted monastrol sensitivity in BLC [214], while *circPVT1* is associated with OS (overall survival) chemoresistance [26]. However, no specific circRNAs have been reported in the drug resistance of HNC. In the near future, circRNAs may be identified as having an important regulatory role in the mechanism of tumor resistance in HNCs.

6. Expression of non-coding RNAs is associated with overall survival in HNC

To investigate the clinical significance of the above dysregulated non-coding RNAs in HNC, we analyzed survival in HNC comparing the levels of 23 different non-coding RNAs in tumor samples (eight lncRNAs and 15 miRNAs). Transcriptome data from The Cancer Genome Atlas database showed a significant difference in survival between high and low expression of *miR-125b*, *miR-200b*, *miR-206*, *miR-654-5p*, and *lncNEAT1* (Fig. 4), confirming the important role of these non-coding RNAs in the drug resistance of HNC.

7. Future perspectives

Non-coding RNAs have been found to be closely related to genomics, biogenesis, mechanism of genic network regulation, signal pathway participation, in vitro or in vivo experimental model phenotypes, and disease abnormality in human cancers. Elucidating the biological role of non-coding RNA, especially in the mechanism of drug resistance, can provide new approaches for identifying novel diagnosis markers and effective treatment targets. However, many integrated landscapes of non-coding RNAs in regulating drug resistance remain unclear and should be extensively studied. Understanding the regulatory mechanisms of non-coding RNAs in the drug resistance of cancer is of great significance to help identify the best treatment methods for patients, improve the sensitivity of chemotherapeutics as

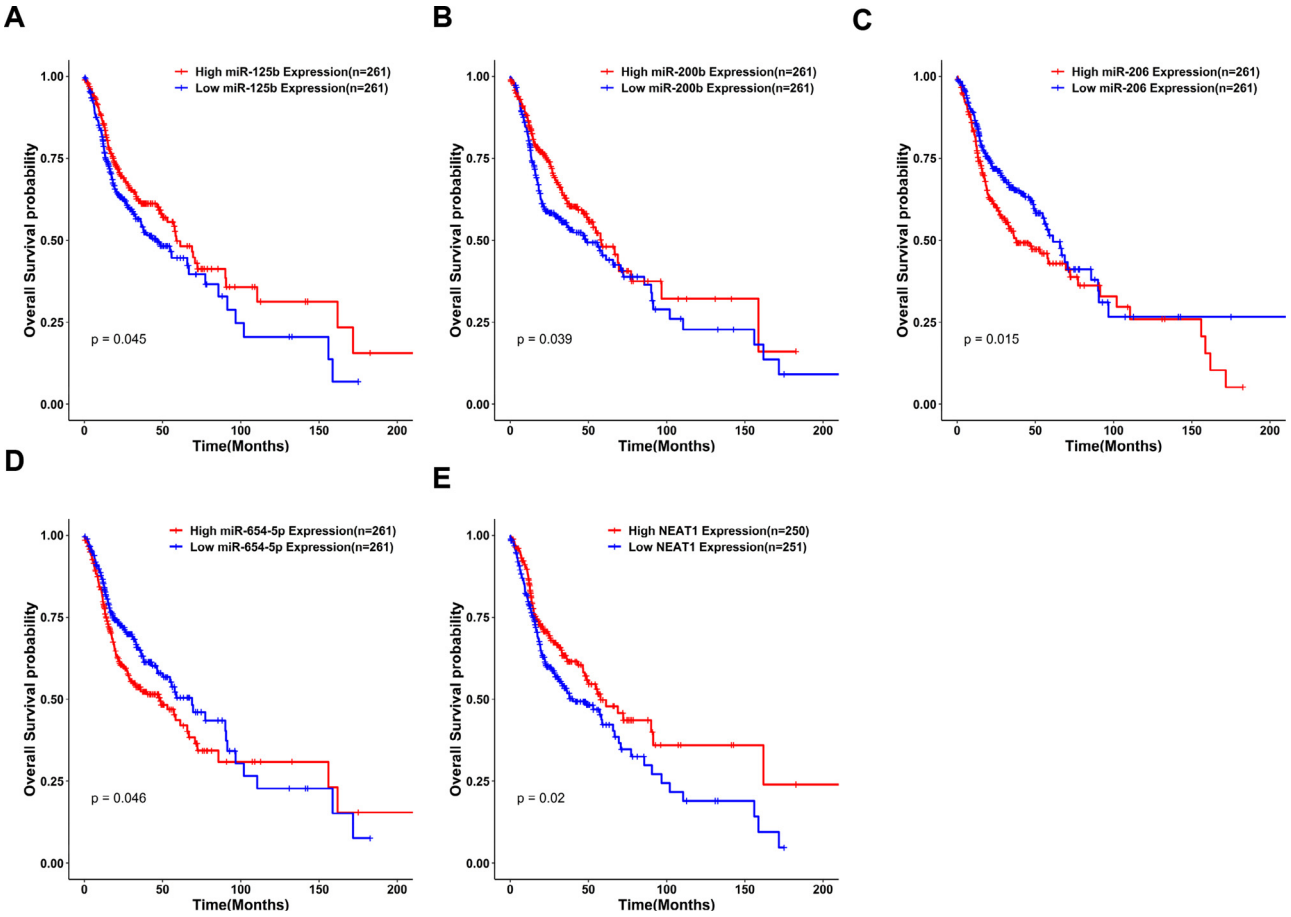

Fig. 4. Survival analysis of HNSCC patients with different *miR-125b*, *miR-200b*, *miR-206*, *miR-654-5p*, and *lncNEAT1* levels in tumor samples. Kaplan–Meier analysis used transcriptome data for HNSCC from TCGA (The Cancer Genome Atlas, updated on Sept. 6, 2018). a. *miR-125b* levels (522 samples). b. *miR-200b* levels (522 samples). c. *miR-206* levels (522 samples). d. *miR-654-5p* levels (522 samples). e. *lncNEAT1* levels (501 samples).

well as the clinical cure rate and overall survival, and reduce the personal economic burden.

Recent studies have suggested that autophagy is involved in the chemoresistance of cancer, and the role of non-coding RNAs in regulating autophagy has also attracted extensive attention [155,215,216]. Autophagy inhibitors combined with the cytotoxic drug chloroquine and its derivative hydroxychloroquine have been approved to treat refractory cancers. Although the cancer drug resistance mechanisms of the interaction between autophagy and non-coding RNA remains obscure, it provides a wide research space to elucidate the mechanisms of cancer chemotherapy.

With the development of methylated RNA immunoprecipitation sequencing, recent studies have confirmed that N^6-methyladenosine (m^6A) has an important role in the occurrence and development of tumors by accelerating the processing time of precursor mRNA as well as the transport and nucleation of mRNA in cells [217]. Additionally, m^6A methylation affects drug resistance in NSCLC [218], cervical squamous cell carcinoma [219], and PAC [220]. Increasing evidence also suggests that m^6A modification of non-coding RNAs has an important role in human disease [221–223]; whether it is involved in tumor drug resistance is yet to be confirmed, but it provides insights for the further study of the important role of non-coding RNAs associated with m^6A regulators in HNC and other chemoresistant tumors.

8. Conclusions

In summary, chemotherapy is an important part of the comprehensive treatment of tumors. However, chemotherapy resistance considerably restricts the success of clinical treatments for HNC [224]. The dysregulation of non-coding RNAs has a major role in regulating the main mechanisms currently known to causing HNC drug resistance. Abnormal expression both of miRNAs and lncRNAs can indeed affect the main cellular pathways or the expression levels of multiple genes, which directly regulates the emergence of chemotherapy resistance in HNC. In addition, miRNAs and lncRNAs can influence HNC cell survival, stemness, and EMT, mediating chemoresistance. In in vivo experiments, researchers also confirmed that selective regulation of miRNA and lncRNA expression can partially improve the sensitivity of HNC to chemotherapy. New drug targets may be explored through verifying reliable miRNA and lncRNA biomarkers associated with chemoresistance. Undoubtedly, further investigation of their precise mechanism and function should lead to revolutionary changes in cancer genic therapy targeting RNA [225]. Additionally, human papillomavirus (HPV) was shown to be associated with HNC [2,226]. Compared with HPV-negative patients, HPV-positive patients responded better to treatment and had a more favorable prognosis [2,227]. However, the relationship between non-coding RNAs and drug resistance in HPV-positive HNC patients has not been reported.

Authors' contributions

WG, YYW and CMA conceived this manuscript. YLZ, MN, YL, and HZL collected and prepared the related references. FSD, LD, and XWZ drafted the manuscript. XWZ and RH performed bioinformatics analysis. YJG drawn the figures. YZ, SXW and WLH supervised and revised the manuscript. All authors read and approved the final manuscript.

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Consent for publication

The content of this manuscript has not been previously published and is not under consideration for publication elsewhere.

Availability of data and materials

Not applicable.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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