

Non-coding RNA in drug resistance of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) has been one of the most highly lethal cancers. The acquisition of drug resistance accounts for the majority of poor effects of chemotherapy in HCC. Non-coding RNAs (ncRNAs) including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNA (circRNA) have been well-documented to participate in cancer occurrence and progression. Recently, multiple studies have highlighted the key roles of ncRNAs in chemoresistance of HCC. In addition, accumulating evidence has demonstrated that they can serve as biomarkers in diagnosis, treatment and prognosis of HCC. In this review, we first overviewed up-to-date findings regarding miRNA and lncRNA in drug resistance of HCC, then summarized specific mechanisms that they modulate chemoresistance of HCC, and finally discussed their potential clinical application in overcoming the obstacle of HCC chemoresistance in the future.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancer and the second leading cause of cancer-related deaths among males worldwide, which is largely caused by chronic hepatitis B virus (HBV) infection[1]. In parts of western countries, the mortality of HCC continues to grow and seriously affects public health[1]. In general, many treatments are curative for early HCC, such as transplantation, surgical resection and chemotherapy[2]. However, the absence of obvious early symptoms results in most HCC cases being first diagnosed at advanced stage. The principal therapeutic agent for advanced HCC, sorafenib, is greatly limited by its drug-resistance[3, 4].

Non-coding RNAs (ncRNAs) refers to RNAs that do not encode proteins. It is well recognized that non-coding RNA makes up a vast majority of cellular RNAs,

accounting for greater than 90% of human RNAs[5]. Recent studies have shown that ncRNAs, just as important as proteins, act as underlying players in multiple cellular processes, such as cell proliferation, migration, apoptosis and angiogenesis and immune response[6]. Non-coding variants are closely linked to most of common diseases, such as human cancers[7]. Additionally, ncRNAs are involved in drug resistance in multiple types of cancer including HCC[8]. The majority of ncRNAs involved in drug resistance are microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)[9]. MicroRNAs are a class of non-coding single stranded RNA molecules, which are constituted by approximately 22 nucleotides. Recent studies have found an association between miRNAs and drug resistance in HCC[10-14]. Long non-coding RNAs are ncRNAs with a length more than 200 nucleotides, which have been shown to interplay with multiple 'biological elements' including DNA, RNA and protein[15]. Through these approaches, lncRNAs exert their effects in various physiological and pathobiological processes like autophagy and metastasis[16-18]. Additionally, lncRNAs also mediate chemoresistance of HCC, offering a new diagnostic marker and therapeutic target for HCC[19, 20]. In addition to miRNA and lncRNA, another type of noncoding RNA – circular RNA (circRNA) has been recently entered into the eyes of researches and scholars. It has been reported to act as a sponge for miRNAs, thereby participating in a series of biological and pathological processes as well as drug resistance[21]. Herein this review summarized the relationship between ncRNAs and drug resistance of HCC.

2. MicroRNAs

2.1 microRNA and multi-drug resistance

2.1.1 Multidrug resistance (MDR)

During the long-term of traditional chemotherapy for HCC, MDR occurs frequently, leading to the relapse of cancer and intractable tumor[22]. Many mechanisms contribute to this resistance. One is that cancer cells enhance the ability of the efflux of hydrophobic cytotoxic drugs[23], partly through overexpression of ATP-binding cassette (ABC) transporters family, including P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP)[24-27], and decrease the uptake of hydrophilic drugs like cisplatin[28]. Recent investigations have shown that 170 kd membrane glycoprotein (170 GP) also has a close relationship with MDR[29]. Another crucial mechanistic branch leading to MDR is resistant to cell apoptosis. For example, wild-type p53 (*wt-p53*) gene re-sensitizes Bel-7402 cells to VCR chemotherapy[30]. Furthermore, *wt-p53* regulates expression of genes of enzymes to mediate function such as activation of pro-drugs, inactivation of active agents, DNA damage repair, modification of stem cells, metabolic alterations and microenvironment change[14, 23, 28, 31, 32]. Various kinds of pathways are related to chemoresistant phenotypes in tumor such as TRPC6/calcium/STAT3 pathway in HCC[33].

2.1.2 Dysregulated miRNAs related with MDR in the treatment of HCC (Table 1)

2.1.2.1 Downregulated miRNAs in HCC

MiR-122 could not only adverse to cisplatin resistance in cisplatin-treated

HepG2 cells[34], but also make HCC cells re-sensitize to adriamycin and vincristine by down-regulating MDR related genes, such as *MDR-1*, *MRP*, *GST-pi*[35]. In another study, Wu *et al.* have found a novel regulatory pathway (Hnf4alpha/miR-122/GALNT10) that could increase sensitivity of cancer cells to doxorubicin and sorafenib[36]. MiR-223 could decrease expression of ABCB1 at both mRNA and protein levels, which could decrease doxorubicin IC50 dose of HCC cells[37]. MiR-216b regulated MDR of HCC via mediating modification of autophagy through HIF-2alpha-MALAT1-miR-216b axis[38]. One study has found that miR-27a might reverse chemoresistance in HCC by inhibiting FZD7/beta-catenin pathway[39]. MiR-612 mediated the function of anti-MDR also through beta-catenin pathway, and finally relieved 5-fluorouracil and cisplatin resistance[40]. Furthermore, miR-34a could also re-sensitize the effect of radiotherapy by inhibiting LDHA[41]. Zhao *et al.* demonstrated that miR-491-3p/Sp3/ABCB1 axis could offer a new pathway for chemotherapy of HCC[42]. Upregulation of miR-503 suppressed HCC cells proliferation, sensitized HCC cells to chemotherapeutic agents like 5-fluorouracil (5-FU)[43], moreover, reversed adriamycin and cisplatin resistance[44, 45]. Besides, miR-137[46], miR-205-5P[47] and miR-27b[48] also have shown a low expression and close correlation with chemoresistance in HCC. Let-7 family consists of 11 closely related genes. Most of them acted as tumor suppressor like Let-7g[49]. Let-7g increased the effectiveness of fluorouracil in treating Bel-7402/5-Fu by targeting on the *HMGA2* gene. However, some Let-7 family members were upregulated in certain tumors and promoted tumor progression, like Let-7a in HCC[50]. Besides, miR-199a could not only increase sensitivity to cisplatin via enhancement of autophagy by targeting autophagy-associated gene 7(*ATG7*)[51], but also increased doxorubicin sensitivity of HCC cells by regulating mammalian target of rapamycin (mTOR) and c-Met[52].

2.1.2.2 Upregulated miRNAs in HCC

MiR-21 plays a vital role in modulating anti-tumor effect of 5-FU and interferon (IFN) - α on HCC cell lines and clinical patients with HCC[53]. The team of Wang XJ suggested that miR-183 promoted MDR in HCC cells by regulating miR-183-IDH2/SOCS6-HIF-1 α feedback loop. Both miR-183 knockdown and SOCS6 overexpression sensitized BEL-7402/5-FU cells to 5-FU[54].

2.2 MicroRNAs mediate single drug resistance of HCC (Table 2)

2.2.1 microRNAs and sorafenib

At present, acquisition of sorafenib resistance is a primary limitation of sorafenib-based chemotherapy. MiR-338-3p was proved to sensitize sorafenib in HCC by down-regulating hypoxia-induced factor 1alpha, which is significant for hypoxia signaling pathway[55]. Additionally, miR-193b increased the sensitivity of HCC cells to sorafenib[56]. While, miR-494 increased sorafenib resistance to HCC cells[57]. MiR-34a was reported to increase the effect of sorafenib in HCC cells via direct suppression of *Bcl-2*[58]. Besides, Xia *et al.* found that *SMAD7* (one of the TGF-beta type 1 receptor antagonist) and *PTEN* were two functional targets of miR-216a/217. By targeting *PTEN* AND *SMAD7*, miR-216a/217 activated the PI3K/Akt and TGF-beta pathways, thereby promoting drug resistance and recurrence of liver

cancer[59].

2.2.2 microRNAs and cisplatin

Apoptosis is a critical underlying mechanism contributing to cisplatin resistance. Recently, numerous studies have shown that microRNAs work in regulating cisplatin resistance *via* targeting apoptosis-associated signaling pathways. For instance, miR-363 reverses cisplatin resistance of HCC cell by directly targeting 3'-UTR of Mcl-1[60]. Tumor protein p53-induced nuclear protein 1(*TP53INP1*) promotes the activity of p53, which has confirmed to be related with tumor cell apoptotic progression[61-63]. MiR-182 expression was negatively correlated with *TP53INP1* both *in vitro* and *in vivo*[64]. In addition, miR-130a increased drug resistance[65]. Sulforaphane(SFN), one of the best anticancer plant active substances discovered in vegetables, could prevent apoptosis in BALB/c mice by activating the defensive response that mediated by NF-E2-related factor 2 (Nrf2), revealing a underlying relationship between Nrf2 and cell apoptosis[66]. Besides, miR-340 has the ability of reversing cisplatin resistance by regulating Nrf2-dependent antioxidant pathway, supporting that miR-340 may be a potential candidate for treating cisplatin resistance of HCC[67]. Upregulation of miR-33a-5p also increased the sensitivity of HCC cells to cisplatin[68].

2.2.3 microRNAs and 5-Fluorouracil

MiR-141 reversed the resistance of HCC cells to 5-fluorouracil *via* the Nrf2-dependent antioxidant pathway[69]. Yang *et al.* reported that overexpression of miR-195 markedly decreased the level of anti-apoptotic protein Bcl-w, and improved the sensitivity of 5-FU in HCC[70]. Furthermore, downregulation of SRSF2 (a splicing factor) could induce apoptosis[71]. By repressing SRSF2, DNA methylation-regulated change the expression of miR-193a-3p, consequently increased the 5-FU resistance of HCC cells[72].

2.2.4 other microRNAs involved in drug resistance in HCC

Apart from those microRNAs mentioned above, miR-106a, miR-215, miR-23a, miR-20a, miR-146a, miR-539, miR-31, miR-26 and miR-33a-5p also show underlying ability to regulate resistance during the treatment of HCC. While, miR-26 reverses the effect to doxorubicin sensitivity[73]. In addition, inhibit the expression of miR-106a offered HCC patients a novel treatment strategy[74]. Adriamycin (ADM) also named doxorubicin is a frequent chemotherapy medication utilized to treat multiple types of cancers. Recent study indicated that upregulation of microRNA-215 resulted in insensitivity to ADM by directly targeting dihydrofolate reductase (DHFR) and thymidylate synthase (TS)[75]. However, overexpression of miR-31 exerted opposite effect[76]. MiR-23a could enhance the anti-tumor effect of etoposide in HCC by inhibiting topoisomerase 1 expression[77]. MiR-20a resensitized HCC cells to radiotherapy via PTEN/PI3K/Akt pathway[78]. MiR-146a regulate the effect of interferon-alpha (IFN-alpha) to HCC cells by mediating SMAD4[79]. Additionally, miR-539 induced HepG2 cells apoptosis and remarkably overcame arsenic trioxide resistance[80].

3. LncRNAs (Table 3)

In recent studies, lncRNAs are widely recognized as crucial regulators in suppressing tumor and oncogenesis, and emerge as potentially vital mediators in regulating drug resistance through modulation of apoptosis, drug efflux system, drug metabolism, DNA repair, and EMT[81-83]. A new study finds that ncRNAs including lncRNAs can participate in drug resistance mediation by controlling the function of cancer stem cells (CSCs)[84]. Li *et al.* demonstrated that lncARSR was involved in doxorubicin resistance during the treatment of HCC. By knockdown of lncARSR, *PTEN* expression was decreased whereas PI3K/Akt pathway was activated. Thus, sensitized HCC cells reacted with the resistance of doxorubicin[85]. linc-VLDLR contributed to improve drug resistance of HCC patients by regulating chemotherapeutic agents transport, in other words, by modulating expression of drug transporter genes, like *ABCG2* (ATP-binding cassette, subfamily G member 2), leading the development of sorafenib-resistance, but decline the viability of cells[86]. As we all know, TGF beta is a key factor related with drug resistance of human cancers. Long non-coding RNA ribonucleic acids-ROR (lincRNA-ROR) is a functional player in chemoresistance during the treatment of chemotherapy. Recent study showed that TGFβ selectively enriched linc-RoR within extracellular vesicles, thereby promoting HCC chemoresistance[87]. Tsang, W. P. and T. T. Kwok have found that knockdown of H19 by transfecting antisense H19 oligonucleotides suppressed the expression of multi-drug resistance 1 (*MDR1*) gene as well as its protein product P-glycoprotein (P-gp), and increased doxorubicin sensitivity in both R-HepG2 cells and HepG2 parent cells, which was partially due to the regulation of *MDR1* promoter methylation by H19[88]. Xiong *et al.* provided a new insight into the function of HULC/USP22/Sirt1/protective autophagy pathway and demonstrated the capacity of lncRNA HULC to decrease chemosensitivity of HCC cells. To be specific, HULC upregulated ubiquitin-specific peptidase 22 (USP22) through down-regulating three microRNAs and stabilizing silent information regulator 1 (Sirt1) protein. Therefore, triggered protective autophagy was harmful for patients with HCC[89]. Taurine up-regulated gene 1 (*TUG1*) is a long non-coding RNA that was identified to be related with tumor cells apoptosis and was upregulated in adriamycin-resistant cells. Yang *et al.* found that down-regulation of *TUG1* attenuated the resistance of HCC cells to chemotherapy *via* suppressing the expression of *MDR1* and P-gp. In addition, after transfected with *TUG1* siRNA and treated with adriamycin, SMMC-7721/ADM and HepG2/ADM cells showed higher apoptosis rate[90]. Furthermore, HANR, NR2F1-AS1 and HOTAIR were lncRNAs up-regulated in HCC tissue. Down-regulation of HANR enhanced chemosensitivity to doxorubicin in HCC cell lines[91], NR2F1-AS1 regulated HCC oxaliplatin resistance by targeting miR-363-ABCC1 pathway[92], and knockdown of lncRNA HOTAIR sensitized HCC cells to cisplatin through regulating the STAT3/ABCB1 signaling pathway[93]. Besides, Schmitt *et al.* suggested that lncRNAs can be regulated by p53. Thus, p53 modulated lncRNAs may be one of the mechanisms for drug resistance in HCC[94]

4. Conclusions

Clearly, drug resistance is the one that causes the most trouble during the therapy of HCC in clinic settings and need urgent solution. Non-coding RNAs including miRNAs, lncRNAs and circRNAs are suggested to be the potential promising therapeutic targets for overcoming drug resistance in the treatment of HCC. Advanced experimental techniques including RNA-sequencing, CRISPR screens, genome wide association studies and high-throughput studies allow characterizing novel ncRNA roles in HCC drug resistance. Molecular mechanisms of ncRNAs in HCC constitute a complicated regulatory network (Figure 1). While, a large biological signal pathway of ncRNAs involved in drug resistance are still unknown. More mechanisms and functions of chemoresistance-related ncRNAs need to be further mined for advance of HCC therapy, which may offer new approaches to reverse drug resistance. Interestingly, this paper finds that some microRNAs belong to same family but own opposite effects in regulating the development of cancer, like Let-7 family. Characterising the underlying roles of those microRNAs may be propitious to HCC treatment. Recently, exosomes are found to have a large content of miRNAs, which brings a bright research prospect. In addition, the knowledge of the emerging functions of lncRNAs and circRNAs in drug resistance or other aspects in cancer are only the tip of the iceberg. Some reports have suggested that lncRNAs and circRNAs may act as sponge for miRNAs, thus playing roles in drug resistance. The evidence of ncRNAs in clinical application is still insufficient. More clinical trials need to be further launched in the future. We believe that ncRNAs combine with chemotherapy will be an effective strategy for advanced liver cancer.

5. Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

6. Authors' Contribution

Bisha Ding, Weiyang Lou: main text; Liang Xu: illustration; Weimin Fan: concept, discussion.

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Table 1. Summary of miRNAs involved in multiple drug resistance in hepatocellular carcinoma

Dysregulation	miRNA	Pathway/ Target	Corresponding drugs	Refs
Downregulated	miR-122	MDR-1, GST-pi, MRP, Bcl-w, cyclinB; Hnf4alpha/miR-122/GALNT10 pathway	adriamycin; vincristine; sorafenib; doxorubicin; cisplatin	[34-36]
	miR-223	ABC1	doxorubicin; paclitaxel	[37]
	miR-216b	HIF-2alpha-MALAT1-miR-216b	5-Fu; et al	[38]
	miR-27a	FZD7/beta-catenin pathway	5-Fu; et al	[39]
	miR-34a	Bcl-2	Sorafenib; radiation	[58]
	miR-612	Wnt/beta-catenin signaling	cisplatin; 5-Fu	[40]
	miR-491-3p	miR-491-3p/Sp3/ABCB1 axis	doxorubicin; vinblastine	[42]
	miR-503	EIF4E	5-Fu; adriamycin; cisplatin	[43-45]
	miR-137	FBI-1	adriamycin; et al	[46]
	miR-205-5P	PTEN/JNK/ANXA3 pathway	5-Fu; et al	[47]
	miR-27b	p53; CYP1B1	doxorubicin; Sorafenib; epirubicin	[48]
	Let-7 g	HMGA2 gene	5-Fu; et al	[49]
	miR-199a (3p/5p)	ATG7; mTOR and c-Met	5-Fu; doxorubicin	[51, 52]
	Upregulated	Let-7a	caspase-3	interferon-gamma; doxorubicin; paclitaxel Interferon-alpha;
miR-21		PETN, PDCD4	5-Fu; cisplatin	[34, 53]
miR-183		IDH2/SOCS6-HIF-1 Alpha	5-FU; et al	[54]
miR-216a/217		PTEN; SMAD7	sorafenib	[59]

Table 2. Summary of other miRNAs involved in single drug resistance in hepatocellular carcinoma

Drugs	miRNA	Pathway/ Target	Dysregulation	Refs
sorafenib	miR-338-3p	HIF-1 alpha	Downregulated	[55]
	miR-193b	Mcl-1	Downregulated	[56]
	miR-494	PTEN, PI3K and p-Akt	Upregulated	[57]
cisplatin	miR-363	Mcl-1	Downregulated	[60]
	miR-182	TP53INP1	Upregulated	[64]
	miR-130a	Wnt/beta-catenin	Upregulated	[65]
	miR-340	Nrf2-dependent antioxidant pathway	Downregulated	[67]
5-FU	miR-33a-5p	/	Downregulated	[68]
	miR-141	Nrf2-Dependent Antioxidant Pathway	Upregulated	[69]
	miR-195	BCL-w	Downregulated	[70]
doxorubicin	miR-193a-3p	SRSF2	Upregulated	[72]
	miR-26	ULK1	Downregulated	[73]
gemcitabine	miR-106a	PDGF-D/miR-106a/Twist1 pathway	Downregulated	[74]
adriamycin	miR-215	DHFR and TS	Upregulated	[75]
	miR-31	NDRG3	Downregulated	[76]
etoposide	miR-23a	TOP1	Upregulated	[77]
radiation	miR-20a	PTEN/PI3K/Akt Signaling Pathway	Upregulated	[78]
Interferon-alpha	miR-146a	SMAD4	Upregulated	[79]
Arsenic trioxide	miR-539	Bcl-2 and Bcl-xL	Downregulated	[80]

Table 3. Dysregulated lncRNAs involved in drug resistance in HCC

LncRNA	Expression in HCC	Drug	Mechanism	Refs
lncARSR	Upregulated	Doxorubicin	Modulating PTEN-PI3K/Akt pathway	[85]
lincRNA-VLDLR	Upregulated	Sorafenib, camptothecin, doxorubicin	Reducing expression of ABCG2	[86]
lincRNA-ROR	Upregulated	Sorafenib	Response to TGF- β	[87]
H19	U[regulated	Doxorubicin	Inducing P-glycoprotein expression and regulating MDR1 promoter	[88]

HULC	Upregulated	Oxaliplatin, 5-fluorouracil, pirarubicin	methylation Triggering autophagy via stabilizing Sirt1	[89]
TUG1	Upregulated	Adriamycin	Promoting expression of P- glycoprotein and MDR1	[90]
HANR	Upregulated	Doxorubicin	Regulating the phosphorylation of GSK3 β	[91]
NR2F1-AS1	Upregulated	Oxaliplatin	Targeting miR- 363-ABCC1 pathway	[92]
HOTAIR	Upregulated	Cisplatin	Activating STAT3/ABCB1 pathway	[93]

Figure 1 legend. NcRNAs involved in drug resistance of hepatocellular carcinoma. Hepatocellular carcinoma (HCC) largely caused by chronic hepatitis B virus (HBV) infection, and the effect of chemotherapy was seriously limited by drug-resistance. A lot of ncRNAs are involved in drug resistance of HCC. These ncRNAs can mediate the sensitivity of single-anti-tumor drug or multi-anti-tumor drug of HCC, and the molecular mechanisms constitute a complicated network machinery.

Figure 1

