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Competitive endogenous network of lncRNA, miRNA, and mRNA in the chemoresistance of gastrointestinal tract adenocarcinomas

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ABSTRACT

Chemotherapy is one of the main therapeutic strategies used for gastrointestinal tract adenocarcinomas (GTAs), but resistance to anticancer drugs is a substantial obstacle in successful chemotherapy. Accumulating evidence shows that non-coding RNAs, especially long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), can affect the drug resistance of tumor cells by forming a ceRNA regulatory network with mRNAs. The efficiency of the competing endogenous RNAs (ceRNAs) network can be affected by the number and integrality of miRNA recognition elements (MREs). Dynamic factors such as RNA editing, alternative splicing, single nucleotide polymorphism (SNP), RNA-binding proteins and RNA secondary structure can influence the MRE activity, which may in turn be involved in the regulation of chemoresistance-associated ceRNA network by prospective approaches. Besides activities in a single tumor cell, the components of the tumor micoenvironment (TME) also affect the ceRNA network by regulating the expression of non-coding RNA directly or indirectly. The alternation of the ceRNA network often has an impact on the malignant phenotype of tumor including chemoresistance. In this review, we focused on how MRE-associated dynamic factors and components of TME affected the ceRNA network and speculated the potential association of ceRNA network with chemoresistance. We also summarized the ceRNA network of lncRNAs, miRNAs, and mRNAs which efficiently triggers chemoresistance in the specific types of GTAs and analyzed the role of each RNA as a "promoter" or "suppressor" of chemoresistance.

1. Introduction

Gastrointestinal tract adenocarcinomas (GTAs) are the most commonly diagnosed malignancies and a leading cause of cancer death worldwide. GTAs mainly include three major groups, namely colorectal cancer (CRC), gastric cancer (GC) and esophageal squamous cell carcinoma (ESCC). The morbidity and mortality of all of these are among the top 10 for cancers worldwide [1]. Surgery is the primary curative treatment for GTAs, but chemotherapy is widely used treatment for patients who need adjuvant therapy after surgery or who have cancers

Abbreviations: GTA, gastrointestinal tract adenocarcinoma; CRC, colorectal cancer. GC: gastric cancer; ESCC, esophageal squamous cell carcinoma; ncRNA, non-coding RNA; lncRNA, long non-coding RNA; miRNA, microRNA; mRNA, messenger RNA; ceRNA, competitive endogenous RNA; TUG1, taurine up-regulated 1; TYMS, thymidylate synthase; SOX, oxaliplatin; CASC15, cancer susceptibility 15; ABCC1, ATP binding cassette subfamily C member 1; ABC, ATP-binding cassette; PCAT-1, prostate cancer associated transcript 1; CDDP, cisplatin; ZEB1, zinc finger E-box-binding homeobox 1; EMT, epithelial-mesenchymal transition; miRISC, argonaut-containing miRNA-induced silencing complexes; MREs, miRNA recognition elements; 3'UTR, 3' untranslated region; SNP, single nucleotide polymorphism; ADAR, adenosine deaminase acting on RNA; TME, tumor microenvoirnment; CAF, cancer associated fibroblasts; TGF-β, transforming growth factor-β; SDPR, serum deprivation protein response; GRM, gemcitabine; UBC, urinary bladder cancers; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; VEGFR1, endothelial growth factor receptors 1; HIF-1α, hypoxia induce factor-1 α; TEC, Tumor epethelial cells; HA, Hyaluronan; ECM, extracellular matrix; LDHA, lactate dehydrogenase A; PAI1, Plasminogen activator inhibitor 1; IAP, Inhibitor of apoptosis; MTX, methotrexate; RBPs, RNA binding proteins; Bcl-2, B-cell lymphoma 2; SIRT1, sirtuin 1; DOX, doxorubicin; GALNT3, polypeptide N-Acetyl galactosaminyl transferase 3; MUC1, mucin 1 cell surface associated; MEF2, myocyte enhancer factor 2; MEF2D, myocyte enhancer factor-2D; MALAT1, metastasis associated lung adenocarcinoma transcript 1; ATG5, autophagy-related 5; TUSC7, tumor suppressor candidate 7; DESC1, Differentially Expressed in Squamous Cell Carcinoma 1

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of advanced stages. Clinical and preclinical evidence strongly suggests that different chemotherapies including commonly combined therapies and targeted therapies [2] are effective and necessary to treat GTAs.

In addition to certain therapeutic effects, chemotherapeutic approaches applied in GTA treatment usually run into a bottleneck due to intrinsic or acquired drug resistance [3,4]. Intrinsic drug resistance usually occurs in patients receiving therapy for the first time. These patients may be primarily diagnosed with advanced cancer or may primarily receive adjuvant treatment following surgery. By contrast, acquired drug resistance may be developed during the second therapy in relapsed patients. A series of cellular regulatory mechanisms are responsible for the poor response of GTAs to chemotherapy. There are many molecular mechanisms that affect cell resistance such as changes in drug transport and metabolism, variations of drug targets, changes in cell damage and cell death and acquirement of cell stemness [5,6]. All these mechanisms can be regulated by non-coding RNAs (ncRNAs), which has opened a new research horizon in cancer chemotherapy.

Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are common functional ncRNAs. Different modes of interactions between lncRNAs and miRNAs have been reported: miRNA decay of lncRNAs, lncRNAs competing with mRNAs to bind to miRNAs, lncRNAs competing with miRNAs to bind to mRNA, and lncRNAs being shorten to miRNAs [7–9]. All these interactions regulate the expression levels of mRNAs and in turn affect core protein signals, resulting in changes in the physiological functions of cells. However, only lncRNA-miRNA-mRNA network has been widely reported to affect chemotherapeutic response in GTAs. In this network, lncRNAs and mRNAs compete to bind to the same miRNA, an association known as the competitive endogenous RNA (ceRNA) mechanism [10].

In the process of GTA chemoresistance regulated by the ceRNA network, mRNAs act as “effector” molecules; that is, changes in the expression of mRNAs can always alter the expression of their proteins [11], which directly affect the biological processes of cancerous cells that resist anticancer drugs. LncRNAs and miRNAs usually act as “regulators”; however, the regulation of mRNA expression by these two is often in opposition. Therefore, regulating the crosstalk between the abnormal expression of ncRNAs and mRNAs may be a feasible strategy to reverse the resistance of GTA chemotherapeutic drugs and has certain application prospects to overcome chemoresistance.

Hence, in this review, we go into the different roles of “promoter” or “suppressor”, played by lncRNAs and miRNAs in ceRNAs that regulate the chemoresistance of tumor cells. Specially, we focus on the active elements such as the MRE-associated dynamic factors and components of TME that affect the efficiency of the ceRNA network in tumor cells and speculate the potential way of these factors to alter the drug resistance of cells by the regulation of ceRNA network. Importantly, we outline the ceRNA mechanism of the lncRNA-miRNA-mRNA network that has been reported to affect chemoresistance in each group of GTAs. The ncRNAs here may all become new therapeutic targets for overcoming chemoresistance in GTAs.

2. lncRNA-miRNA-mRNA ceRNA network and the corresponding roles of these RNAs in chemoresistance of GTAs

miRNA transcripts of 20-24 single-stranded nucleotides, play essential roles in post-transcriptional regulation. Mature miRNAs are incorporated into Argonaut-containing miRNA-induced silencing complexes (miRISCs), and then bind to a short region of mRNA called a miRNA recognition elements (MREs), which are usually located in the 3′ untranslated region (3′ UTR) of mRNA. The binding of miRNA to an MRE leads to the breakdown or translational repression of the mRNA. Degradation or translational repression of a protein-coding mRNA effects the level of the protein without modifying the gene sequences [12]. One miRNA may bind to different target mRNAs with similar MREs and one mRNA containing different MREs can also be targeted by different miRNAs [13,14]. These characteristics establish the fundamental principle of ceRNAs, such that binding of miRNAs can be competed for by not only an mRNA but also other non-coding RNA transcripts such as lncRNAs with similar MREs [10]. lncRNA, which are more than 200 nucleotides long, do not encode any protein but specifically function as gene regulators at different molecular levels, from chromatin modification to transcription to post-transcriptional modifications [15,16].

Various lines of evidence point to the active involvement of the ceRNA network, via lncRNA-miRNA-mRNA dysregulation, in chemotherapeutic drug resistance in different cancers [17,18]. The mRNA, the final target to be regulated by the ceRNA network, and its protein expression level determine whether the cells are resistant or sensitive to the drug. There are two possible mechanisms through which the ceRNA network can regulate chemoresistance. In the first role, wherein the mRNA acts as a “promoter” of drug resistance, a miRNA would be an ideal target to overcome chemoresistance. In this instance, the miRNA binds to the MRE of a chemoresistance-promoting mRNA to inhibit oncogenic expression via its degradation or translational inhibition. In contrast, the second possible role of an mRNA is that it acts as an “inhibitor” of drug resistance. High expression of a miRNA would be the contributing factor to chemoresistance by downregulating the “inhibitor mRNA” by degrading or terminating its translation by bindng to its MRE. In such cases, the lncRNA becomes an ideal weapon to overcome chemoresistance by providing similar MREs to “sponge” the target miRNA [19,20]. Based on the regulatory role of the lncRNA-miRNA-mRNA network, we can reverse the drug resistance of tumors by precisely targeting "promoters" or introducing exogenous "inhibitors" to improve the sensitivity of tumor cells.

Observed from the cellular and molecular biological levels, the change in mRNA expression effected by the ceRNA network usually affects a series of cellular biological processes to alter chemotherapy resistance. The mechanisms that can lead to chemotherapy resistance in cancer cells mainly include an increase (decrease) in drug efflux (influx), induction of drug inactivation, alterations in the molecular targets of chemotherapeutic drugs, reduction (induction) of apoptotic (anti-apoptotic) gene expression, acquisition of cellular stemness and enhanced ability of cancerous cells to repair anticancer drug-induced DNA damage. For example, resistance to 5-fluorouracil (5-FU) in CRC cells can be regulated by the lncRNA TUG1-miR-197-3p-TYMS ceRNA network. TYMS, a "promoter" effector molecule, is the target of 5-FU. Its high expression will make the cell drug resistant by combining with excessive drug molecules [21]. Reduced expression of TYMS promotes apoptosis and resensitizes the cells [22]. Changes in the expression of lncRNA TUG1 or miR-197-3p can alter the expression of TYMS, which affects drug targets and the process of programmed cell death, and in turn affects drug resistance. Another study showed that CRC cells can regulate the sensitivity to oxaliplatin (SOX) through the lncRNA CASC15-miR-145-ABCC1 ceRNA network. ABCC1, as a "promoter", is a member of the well-known ATP-binding cassette (ABC) transporter family. It promotes intracellular-to-extracellular transport of drugs to help cells acquire drug resistance [23,24]. Both of the high expression of CASC15 and the low expression of miR-145, via CASC15 sponging miR-145 to inhibit its binding with its target ABCC1, will increase the expression of ABCC1 and, in turn, let the cells acquire drug resistance [25]. For instance, lncRNA PCAT-1-miR-218-ZEB1 network can regulate cell resistance to cisplatin (CDDP). The promoter ZEB1 is an activator of epithelial-to-mesenchymal transition (EMT), which increases the resistance of cells to CDDP by increasing cellstemness [26]. In this network, the high expression of PCAT-1 or ZEB1, promotes the drug resistance of cells. In contrast, high expression of miR-218 inhibits ZEB1 protein expression by binding to its mRNA to inhibit EMT and improve CDDP resistance [27]. The above examples illustrate that ceRNA networks of lncRNAs, miRNAs, and mRNAs play roles in the chemoresistance of cancer by affecting important cellular biological processes.

3. Effective dynamics of ceRNA network in chemoresistance

In cells that depend on the ceRNA network as a mechanism for regulating drug resistance, the efficiency of the ceRNA network is the determinant of the final state of chemotherapy. The main factors that affect the efficiency of ceRNA action are the abundance and subcellular localization of miRNAs, lncRNAs and mRNAs as well as the binding efficiency of MREs to miRNAs.

In the ceRNA network, equal quantities of different types of the involved RNA transcripts are required. For this reason, a miRNA's overall target abundance negatively correlates with the miRNA's average repressive strength. The RNAs must also localized in the same compartment for ceRNA network to function normally. ceRNA networks usually function in cytoplasm. In addition to subcellular localization, the number and integrality of MREs have a great effect on ceRNA activity [28]. Disruptions in the normal function of genetic and/or epigenetic factors and processes, such as RNA editing, alternative splicing, single nucleotide polymorphisms (SNPs), RNA-binding proteins and RNA secondary structure, are highly probable events in cancer that play important roles in disrupting the number or integrality of MREs. We analyze the impact of the above factors on the function of the ceRNA network, and hypothesizing that if these alterations occur in the genes involved in chemoresistance, the effect of chemotherapy will be improved by regulating of the ceRNA network (Fig. 1).

3.1. RNA editing

RNA editing is a post-transcriptional process that alters the sequence of an RNA transcript from its source DNA sequence [29]. RNA editing works by different types of mechanisms depending on whether nucleotides get inserted, deleted or converted [30]. The most prevalent type of RNA editing found in higher eukaryotes including humans, is the conversion of adenosine (A) into inosine (I) in double-stranded RNAs (dsRNAs) via the catalytic activity of adenosine deaminase acting on RNA (ADAR) enzymes [31]. Hot-spot targets of A-to-I RNA editing are the introns and 5′/3′ UTRs of mRNAs, which are important features in translation and other gene regulation activities [32]. Therefore, alteration of MRE in 3′ UTR by RNA editing influences the recognition site of miRNAs, leading to notable phenotypes in tumorigenesis as well as in chemoresistance [33,34].

Interestingly, in cancers including GTAs, RNA editing plays a major role in carcinogenesis [35–37]. Although indirect evidence of the potential capability of RNA editing in tumorigenesis has been found in other cancers, the presence of a ceRNA network regulated by RNA editing involved in GTA chemotherapeutic resistance still needs to be explored. It has been reported that cellular proliferation and resistance to methotrexate (MTX), an anticancer drug, is enhanced when ADAR1 improves the expression of dihydrofolate reductase (DHFR) in breast cancer by editing the binding site of miR-25-3p and miR-125a-3p in 3′ UTR s of the DHFR mRNA [38]. Editing in the MREs of lncRNAs also has a marked effect on miRNA-lncRNA interactions, which directly or

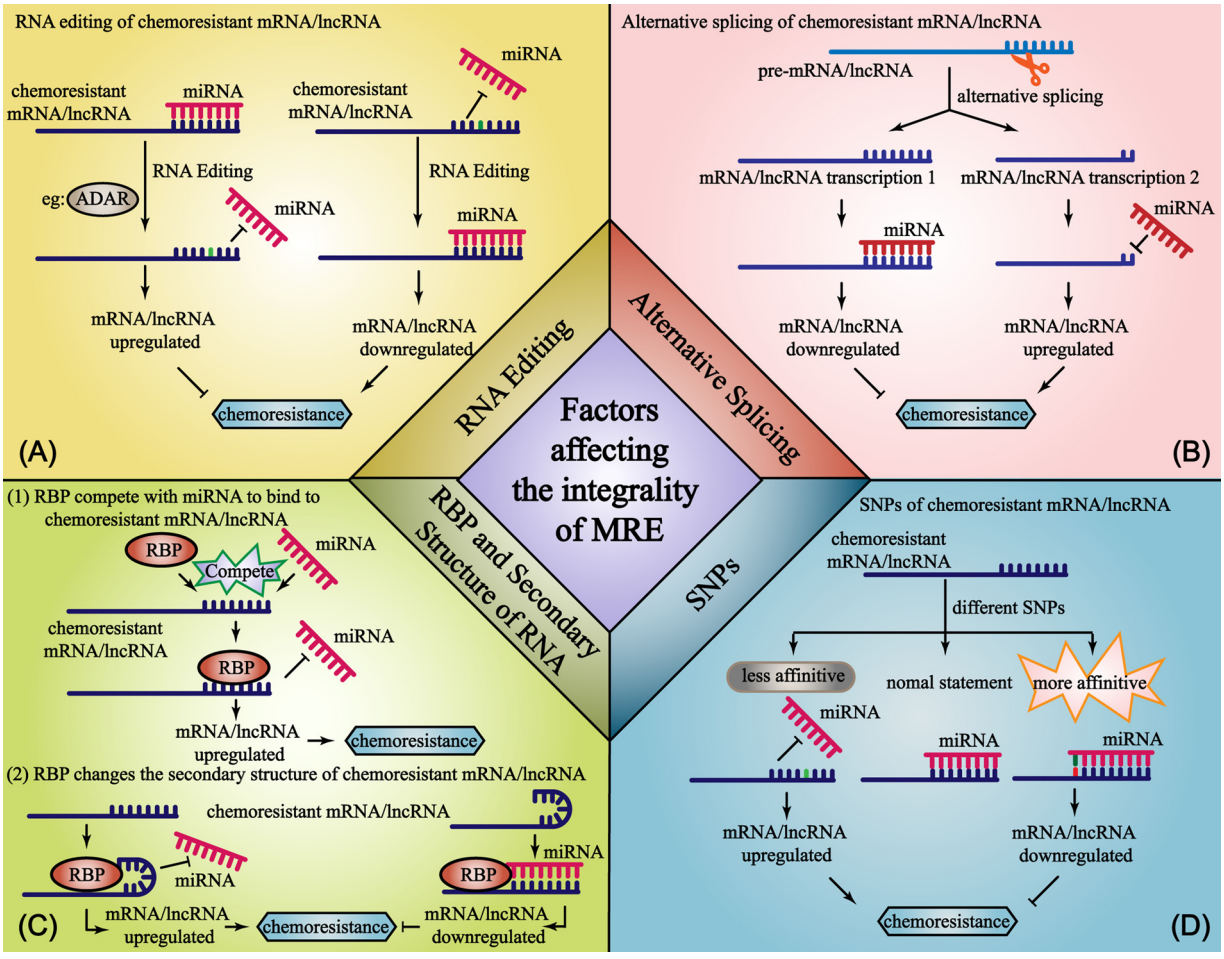

Fig. 1. The dynamic factors regulating MREs affect the ceRNA network and have potential roles in regulating the chemoresistnace in tumor cells.
A) RNA editing in the MREs of mRNAs or lncRNAs can promote chemoresistance by affecting miRNA binding. B) Alternative splicing in mRNA or lncRNA transcripts may promote or hinder the pairing with their respective miRNAs to promote chemoresistance. C) RBP and secondary structure of mRNA/lncRNA affect the binding of a miRNA to its specific MRE, causing chemoresistance. D) Changes in MREs due to SNPs also affect the binding of miRNAs to cause chemoresistance.

indirectly regulate the expression of protein-coding genes responsible for tumorigenesis. Thanks to advancement in high-throughput technologies, lncRNA editing sites present in different species are compiled in the "LNCediting" database. The LNCediting database identified 114814 and 109788 possible editing sites that are responsible for 742855 and 731035 losses and gains of function of miRNA-lncRNA interactions, respectively [39]. This evidence shows that edited and non-edited MREs in mRNAs and lncRNAs may pair with different miRNA to regulate several carcinogenesis functions. There are still some questions that need to be addressed regarding lncRNA-miRNA-mRNA crosstalk in GTAs. This includes the question of whether edited MREs of mRNAs and lncRNAs influence ceRNA crosstalk, which may promote chemoresistance in GTAs, and whether potential therapies based on edited MREs could promote chemosensitivity in GTAs. The possible answers to these questions could help researchers to determine how these hotspots of RNA editing affect lncRNA-miRNA-mRNA interactions and improve the chemotherapeutic outcome of GTAs.

3.2. Alternative Splicing

Alternative splicing produces multiple protein isoforms by altering the components of the transcript. 3′ UTR shortening alters an mRNA transcript, which in turn affects the binding of the mRNA to miRNAs. It has been reported that many genes related to chemotherapy resistance may be alternatively spliced, which may offer a chance to disrupt the ceRNA network. For example, glutamine metabolism is tightly associated with drug resistance in several cancers. It has been reported that targeting glutamine metabolism helps to overcome CDK4/6 resistance [40], and the lack of glutamine will recover the sensitivity of cells to CDDP, the first-line drug of gastrointestinal cancers [41]. Recently, researchers found that the core enzyme of glutamine metabolism, glutaminase, can be regulated by alternative splicing. This generates two transcripts with distinct 3′ UTR displaying totally different affinities to miRNA-23 [42]. It provides a basis for the functional change in the ceRNA network. Thus, the alternative splicing influences the development of tumor resistance.

3.3. RNA binding Proteins and Secondary Structure of RNA Transcripts

RNA-binding proteins (RBPs) play an important role in the regulation of post-transcriptional processes such as RNA splicing, transport, translation and stability. MREs in 3′ UTRs are also hotspots for RNA-binding proteins [43,44]. RBPs can affect the ceRNA complex by altering the structure of the 3′ UTR or by occupying the target site on the mRNA, which may affect its affinity and accessibility to miRNAs [45]. Depending on the association of RBPs with mRNAs, specific RBPs could either enhance or inhibit the binding of miRNAs to MREs, which may lead to various disorders, including cancer [46,47]. The Hu family of RBPs, consisting of ubiquitously expressed HuR (HuA), HuB, HuC and HuD, are important mammalian RBP that can bind to AU-rich elements that are mainly located in 3′ UTR of mRNAs [48]. There is evidence showing the effect of RBPs on the ceRNA interplay responsible for tumorigenesis [49,50], while little is known about its involvement in chemoresistance. Kojima et al [51] reported the binding interaction of an RBP, miRNA and mRNA in paclitaxel-resistant prostate cancer. According to their study, increasing the expression of HuR leads to a decrease in the expression of miR-34a, which upregulates the expression of B-cell lymphoma 2 (Bcl-2) and sirtuin 1 (SIRT1) and results in paclitaxel resistance by reducing cell apoptosis. SIRT1 overexpression is also responsible for CDDP resistance [52]. These findings are supported by a study in colon cancer, that demonstrated that SIRT1 expression is involved in a network with miRNAs to regulate the effect of CDDP chemotherapy [53]. Thus, the expression of SIRT1 is potentially regulated by RBP-miRNA interactions in colon cancer. Another study reported that the translation of the topoisomerase IIα (TOP2A) mRNA is enhanced by HuR and that this mRNA competes with miR-548c-3p. In HeLa cells, the TOP2A expression level is altered by overexpression of miR-548c-3p or inhibition of HuR, and TOP2A controls the cellular response to the anticancer chemotherapeutic agent doxorubicin (DOX) [54]. In addition, binding of proteins may alter the secondary structure of an RNA transcript, which increases or decreases the binding of additional proteins or the binding of miRNAs to its MREs [55,56]. According to Kedde et al, the RBP Pumilios is needed for miR-221/miR-222-mediated repression of the p27 tumor suppressor. Pumilio RNA-binding family member 1(PUM1) binding induces structural changes in 3′ UTR of the p27 transcript that expose a binding site for miR-221/miR-222, efficiently suppressing p27 expression and modulating cell cycle progression [57]. These studies explain the effect of RBPs and secondary structure on miRNA-mRNA interactions. However, the question of whether the miRNA-lncRNA interaction and ceRNA crosstalk involved in chemoresistance is also affected by RBPs and the secondary structure of RNA transcripts still needs to be answered. This transcriptomal landscape provides a basis for researchers to explore and fine-tune the actions of ceRNA transcripts to overcome the hurdle of chemoresistance.

3.4. Single Nucleotide Polymorphism (SNPs)

SNPs in 3′ UTR MRE in miRNA targets, also known as miRSNPs, show a specific mode of miRNA-mRNA regulation in genetic information. SNPs in MREs can destroy, create or/and modify the binding relationship of miRNAs with mRNAs [58,59], thereby resulting in gain or loss of function. A gain or loss of function in 3′ UTR either creates new miRNA-binding sites to reduce protein translation or abolishes miRNA-mRNA binding and results in high protein expression, respectively [60]. For example, Kim and coworkers reported that the rs12373A > C polymorphism in the 3′ UTR of pancreatic adenocarcinoma upregulated factor (PAUF) can increase the binding efficiency of miR-571 and cause suppression of the PAUF gene, which may play a key role in the survival outcome of CRC patients [61]. Another study reported the effect of SNPs on chemoresistance, in which SNP-829C > T near the binding site of miR-24 in the DHFR 3′ UTR results in loss of function. DHFR expression is affected by the interfering of SNPs with the function of miR-24, leading to the overexpression of DHFR and MTX resistance [62]. The examples presented above show that any loss or gain of function due to SNPs in MREs may affect ceRNA crosstalk in cancer as well as chemoresistance.

Although some of the ceRNA efficiency-related factors stated above still lack direct proof of being involved in chemoresistance in GTAs, all this indirect evidence offers a research landscape for researchers to explore the association of the above mentioned dynamics in GTA chemotherapeutic response.

4. Influence of the TME on ceRNA networks and chemoresistance

Current studies show that the crucial role of regulating the efficiency of the ceRNA network is not limited to the internal activities in a single tumor cell, but also includes the bidirectional communications between cells and their microenvironment. The TME is composed of cellular components including cancer associated fibroblasts (CAFs), immune cells, vascular endothelial cells and tumor stem cells [63] and non-cellular components including cytokines, metabolites, growth factors and extracellular matrix proteins [64]. In the internal microenvironment of tumors with fewer or no blood vessels, hypoxia is the most prominent and severe environmental condition [65]. The complex scenes of intercomponent interactions (cells to cells, or stroma to cells) and special conditions (such as hypoxia) in the TME can all affect the working efficiency of the ceRNA network in tumor cells, which in turn will affect the malignant phenotypes of tumors, such as proliferation, invasion, metastasis or chemoresistance. The research in this field is in its infancy, as there are only a few in-depth studies on this subject that have demonstrated the exact mechanism by which the TME affects the

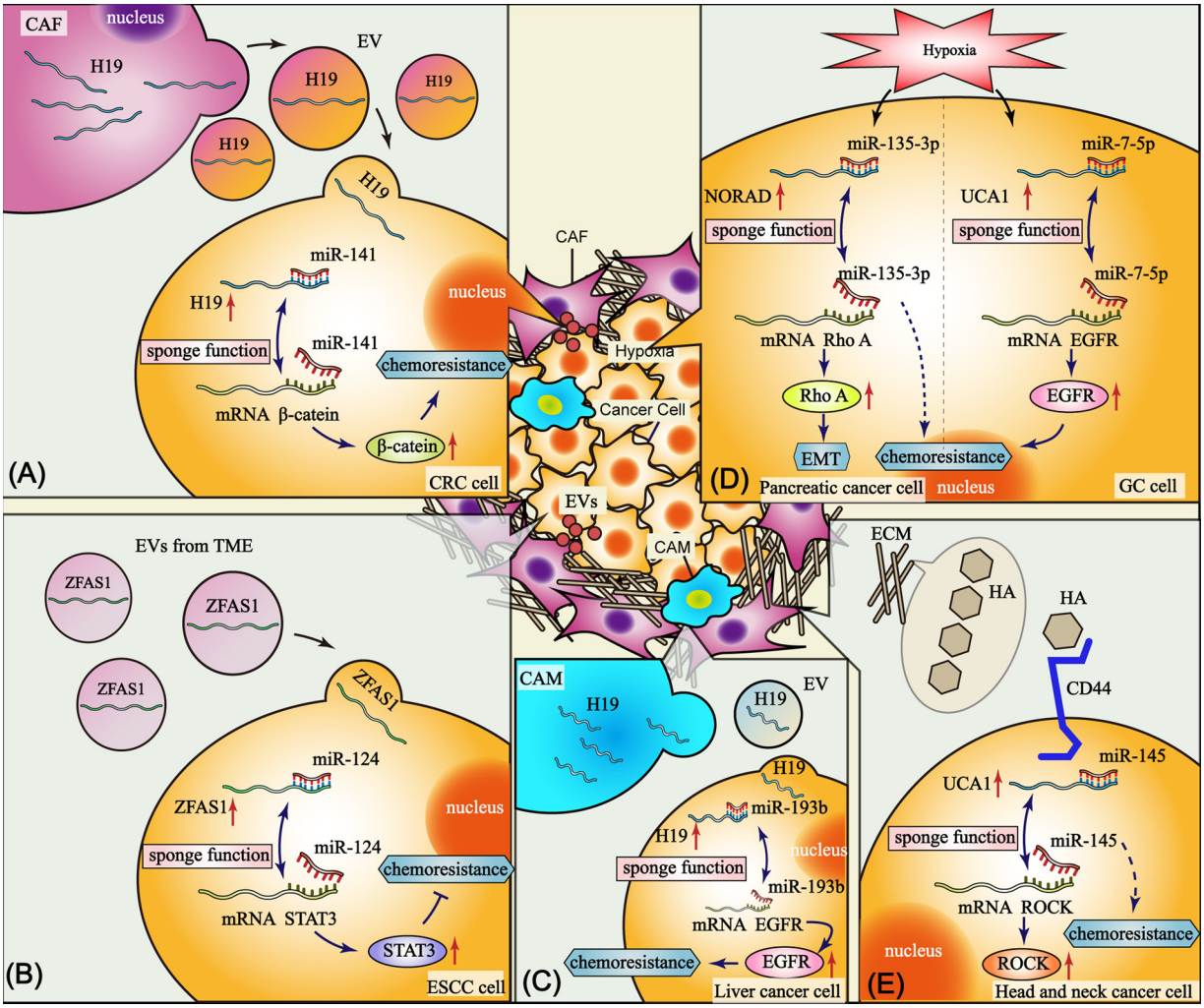

Fig. 2. The components of TME affect the ceRNA networks and have potential roles in regulating the chemoresistance in tumor cells.
A) EVs from CAFs transported H19 into CRC cells and activated the ceRNA network of H19/miR-141/β-catenin to promote the chemoresistance of tumor cells. B) ZFAS1 in EVs from TME was transported into ESCC cells and activated the ceRNA network of ZFAS1/miR-124/STAT3. STAT3 may play a role in reversing the chemoresistance of tumor cells. C) EVs from CAM transported H19 into liver cancer cells and activated the ceRNA network of H19/miR-193b/EGFR. EGFR may play a role in promoting chemoresistance of tumor cells. D) Hypoxia activated two ceRNA networks, lncRNA NORAD/miR-135a-3p/Rho A and UCA1/miR-7-5p/EGFR. MiR-135a-3p may play a role in reversing the chemoresistance of tumor cells. E) The major component of ECM, HA, bound to CD44 and activated the ceRNA network of UCA/miR-145/ROCK. MiR-145 may play a role in reversing the chemoresistance of tumor cells.

function of the ceRNA network in tumors, and even less is known about the TME and the chemoresistance of GTA. Nevertheless, a few studies have shown that the TME affects the expression of non-coding RNAs in tumors, but this change in RNA expression has considerable potential for affecting the efficiency of the ceRNA network.

4.1. TME regulates the working efficiency of ceRNAs to affect the malignant phenotypes of tumors

When the cell components in the TME communicate with tumor cells, they have a chance to impact the efficiency of the ceRNA network in tumor cells. For example, the study of Ren J and colleagues indicated that the lncRNA H19 expressed in colorectal cancer-associated fibroblasts could be encapsulated and in extracellular vesicles (EVs) to enter tumor cells as a sponge for miR-141, thereby attenuating the inhibitory effect of miR-141 on β-catenin, to activate the Wnt/β-catenin pathway. By this mechanism, colorectal cancer cells acquired stemness and chemoresistance to oxaliplatin [66] (Fig. 2A). It is not difficult to see from the above study that EVs are an important medium of information exchange in the TME. In fact, in addition to CAF cells, between other cellular components in the TME and tumor cells, or between tumor cells and tumor cells, the exchanges of biological molecules or information can be completed by releasing EVs, which ultimately influence the functions of tumor cells. For example, a study in esophageal cancer cell lines found that after lncRNA ZFAS1 packed in EVs was incorporated into tumor cells, miR-124 could be bound by ZFAS1 and impaired in its functions, which indirectly weakened its inhibitory effect on its downstream target STAT3 and finally promoted the migration and growth ability of esophageal cancer cells [67] (Fig. 2B). Moreover, STAT3β, one isoform of STAT3, suppresses chemoresistance of cisplatin and 5-fluorouracil and cancer stemness in esophageal cancer [68].

The immune microenvironment is also an important part of the TME. It is composed of many categories of immune cells that can establish crosstalk with tumor cells to affect their internal signaling pathways. Ye Y and its colleagues found that liver cancer-associated macrophages could stimulate the overexpression of lncRNA H19 in liver cancer cells, which was a sponge of miR-193b and in turn hindered the ability of miR-193b to bind its target mRNAs. Thus, the expression of the downstream target genes EGFR, PTEN and KRAS was significantly increased, which promoted the EMT and stemness of liver cancer cells, leading to a worse prognosis [69] (Fig. 2C). Moreover, it was reported that the overexpression of EGFR enhanced the resistance to PARP

inhibitor in hepatocellular carcinoma [70].

In addition to the cellular components in the TME, non-cellular components can also have an impact on tumor cells to affect the efficiency of the ceRNA network. Li H and colleagues indicated that in pancreatic cancer, the hypoxic environment of the tumor induced the upregulation of the lncRNA NORAD, which acted as a sponge of miR-135a-3p to indirectly cause an increase in the expression of miR-135a-3p target Rho A. Rho A is an important downstream molecule of hypoxia and a regulator of EMT (Fig. 2D). This hypoxia-induced functional change in the ceRNA network of NORAD/miR-135a-3p/Rho A ultimately promoted the EMT process of tumor cells [71]. What's more, some research found that enhanced the expression of miR-135a-3p can induce a sensitivity to cisplatin and paclitaxel of tumor cells in ovarian cancer [72], which suggests a potential role of hypoxia-induced ceRNA network containing miR-135a-3p in the regulation of chemoresistance. Yang Z and colleagues also proved that hypoxia could affect a ceRNA network of UCA1/miR-7-5p/EGFR to promote the migration of gastric cancer cells by establishing a hypoxia-tolerant gastric cancer cell line [73]. Hypoxia increased the expression of UCA1 and in turn upregulated the expression of EGFR mRNA, which plays a potential role in tumor chemoresistance (Fig. 2D).

In addition to hypoxia, the review by L.Y.W. Bourguignon noted that hyaluronan (HA), the main active ingredient of extracellular matrix (ECM), could act on the tumor cell membrane receptor CD44 and affect the signaling pathways of microRNAs and lncRNAs to influence the corresponding phenotype of tumor cells [74]. In that review article, he also did a few in vitro experiments that confirmed that in head and neck cancer cell lines, the addition of HA components could promote the high expression of the lncRNA UCA1, relatively low expression of miR-145 (which targets UCA1), and the high expression of the proven target gene ROCK of miR-145 [75] (Fig. 2E). This indicated that HA, a non-cellular component of the microenvironment, could affect the lncRNA/UCA1/miR-145/ROCK ceRNA network in tumor cells, and it was also proven in functional experiments that the alternation of this ceRNA network could affect the invasion and migration ability of tumor cells [74]. What's more, as a tumor suppressor, miR-145 played a role in reversing chemoresistance in many different tumors [76,77]. In short, the communication between TME components and tumor cells can regulate the ceRNA network and in turn affect the malignant phenotype of tumors.

4.2. TME regulates the expression of non-coding RNAs and has the potential to affect the ceRNA network

There are many ways that the tumor microenvironment affects the expression of non-coding RNAs in tumor cells, either through the EVs mentioned above or through core secreted proteins acting on tumor cells to alter their gene expression.

An increasing number of studies have indicated that EVs envelop non-coding RNAs and transport them into the TME as carriers, changing the quantity of RNAs in cells and affecting the development and malignant phenotype of tumors. In addition to the examples given above, there are some other examples where EVs carry non-coding RNA to affect their expression. For example, in a study on epithelial ovarian cancer, the authors found that when EVs secreted from tumor-associated macrophages were cocultured with human umbilical vein endothelial cells (HUVECs), the expression of miR-146b-5p within HUVECs increased and further inhibited the migration ability of endothelial cells to a certain extent [78]. However, two functional lncRNAs, ENST00000444164 and ENST0000043768 packaged in EVs from tumor cells counteracted the enhanced migration ability of endothelial cells induced by miR-146b-5p containing EVs [78]. It is not difficult to see from the above findings that the regulatory effect of the TME on the malignant phenotype of tumors is not limited to tumor cells but can also be realized in other cell components of the TME, such as endothelial cells. A study in colorectal cancer also indicated that EVs derived from CAFs could encapsulate the lncRNA CCAL and transport it into tumor cells, where it activates the β-catenin pathway to make cells resistant to Oxa [79]. Moreover, CCAL has been shown to form a ceRNA regulatory network with miR-149/FOXM1 in gastric cancer to affect the metastasis of gastric cancer [79]. These examples demonstrate that the TME can regulate the content of non-coding RNA in cells via EVs. The alteration of this content has the potential to affect the ceRNA network, and may affect the malignant phenotypes of tumor cells such as drug resistance. However, research in this area still needs to be further explored in GTA.

TGF-β is one of the most common and versatile secreted proteins in the TME. It can be paracrinely secreted by CAFs, endothelial cells, or tumor cells themselves and then binds to the type I and II receptors on the surface of tumor cell membranes to activate the SMAD signaling pathway or SMAD-independent pathways, such as MAPK and PI3K/AKT, or other important tumor-related pathways to affect the malignant phenotype of tumor cells [80]. However, in recent years, studies have found that not all of the mechanisms of paracrine TGF-β are activated and TGF-β can also cause abnormal expression of non-coding RNAs, such as lncRNAs and miRNAs in tumor cells. For example, an in vitro study conducted on breast cancer cell lines and primary cultured fibroblasts derived from breast cancer patients showed that TGF-β secreted by CAFs could activate SMAD2/SMAD3/SMAD4 molecules in tumor cells, and the activated SMADs bound to the promoter region of the lncRNA HOTAIR to promote the transcription and increase the expression of HOTAIR [81]. Moreover, in research on gastric cancer and ovarian cancer, it was found that HOTAIR could play the role of miRNA sponge, weakening the inhibitory effect of miRNAs on other target genes related to chemoresistance, and finally making gastric cancer and breast cancer cells resistant to trastuzumab and cisplatin,respectively [82,83]. Therefore, the secretion of cytokines such as TGF-β into the tumor microenvironment can cause abnormal expression of non-coding RNAs in tumor cells. This abnormality has the potential to change the drug sensitivity of tumor cells by affecting the downstream ceRNA network. In GTAs, there are some reported lncRNAs and miRNAs that can be regulated by TGF-β expression[84–87]. In summary, research on the effect of cytokines secreted by the TME on the function of the ceRNA network in GTAs affecting chemoresistance has considerable prospects.

5. lncRNA-miRNA-mRNA Network in response to chemotherapy of GTAs

5.1. CRC

CRC is the 3rd most commonly diagnosed cancer (10.2% of total cases) and the 2nd leading cause of cancer death (9.2% of total cases) [1]. Chemotherapy for advanced patients or adjuvant chemotherapy following surgery is commonly used as a clinical treatment. However, more than 90% of treatment failures are due to the resistance to chemotherapy [88]. Possible dysregulation of the crosstalk between lncRNAs, miRNAs and mRNAs associated with chemoresistance has been studied in human CRC [89,90]. One of the most studied lncRNAs, H19, has been found to be upregulated in recurrent CRC patients and to act as a "promoter" of 5-FU resistance in CRC cells. Mechanistically and functionally, H19 activates autophagy through SIRT1 to induce cancer chemoresistance. H19 binds to miR-194–5p and competes with SIRT [91]. Thus, miR-194-5p acts as a "suppressor" of 5-FU resistance. SIRTs, which are autophagy elements and members of the NAD + -dependent histone deacetylase family, can also activate autophagy and protect cells from chemoresistance [92]. This study suggests that 5-FU resistance is the result of the crosstalk of H19/miR194–5p/SIRT1-mediated autophagy (Fig. 3) [91]. Another study provides conclusive evidence that polypeptide N-acetyl galactosaminyl transferase 3 (GALNT3) expression is regulated via the linc01296/miR-26a/GALNT3 axis, which in turn modifies O-glycosylation on Mucin 1, cell surface-

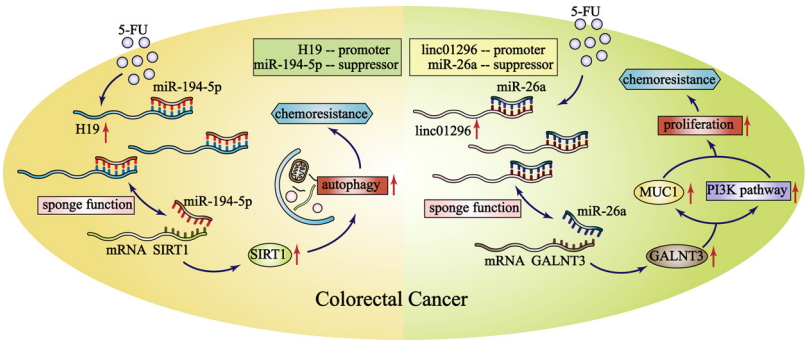

Fig. 3. Dysregulation of the ceRNA network causes chemoresistance in CRC. Left) 5-FU resistance caused via H19/miR194–5p/SIRT1-mediated autophagy. Right) linc01296/miR-26a/GALNT3/MUC1 crosstalk activates the P13 K pathway which increases proliferation to cause chemoresistance to 5-FU.

Table 1
The lncRNA-miRNA-mRNA networks involved in chemoresistance of CRC, GC and ESCC.

Cancer Type	lncRNA as ceRNA	Expression	Sponged microRNA	Targeted mRNA	Drug resistance	Reference
CRC	UCA1 (promoter)	Up	miR-204-5p (suppressor)	CREB1	5-FU	[106]
	XIST (promoter)	Up	miR-124 (suppressor)	SGK1	DOX	[3]
	TUG1 (promoter)	Up	miR-186 (suppressor)	CPEB2	MTX	[107]
	HOTAI (promoter)	Up	miR-218 (suppressor)	VOPP1	5FU	[108]
	SCARNA2 (promoter)	Up	miR-342-3p (suppressor)	EGFR/BCL2	SOX/5FU	[109]
	ENST00000547547 (suppressor)	Down	miR-31 (promoter)	ABCB9	5-FU	[110]
	MEG3 (suppressor)	Down	miR-141 (promoter)	PDCD4	SOX	[111]
	ANRIL (promoter)	Up	Let-7a (suppressor)	ABCC1	5-FU, SOX	[112]
	Linc00152 (promoter)	Up	miR-193a-3p (suppressor)	ERBB4	SOX	[113]
	H19 (promoter)	Up	miR-194-5p (suppressor)	SIRT1	5-FU	[91]
	linc01296 (promoter)	Up	MiR-26a (suppressor)	GALNT3	5-FU	[65]
GC	BLACAT1 (promoter)	Up	miR-361 (suppressor)	ABCB1	SOX	[114]
	HOTAIR (promoter)	Up	miR-17-5p (suppressor)	PTEN	CDDP, ADR, 5-FU	[115]
	HOTAIR (promoter)	Up	miR-34a (suppressor)	Rictor	CDDP	[97]
	lncR-D63785 (promoter)	Up	miR-422a (suppressor)	MEF2D	DOX	[100]
	MALAT1 (promoter)	Up	miR-23b-3p (suppressor)	ATG12	VCR	[116]
ESCC	TUSC7 (suppressor)	Down	miR-224 (promoter)	DESC1	CDDP	[104]
	PART1 (promoter)	Up	miR-129 (suppressor)	Bcl-2	Gef	[105]

associated (MUC1). O-glycosylated MUC1 inactivates the P13 K/AKT pathway, which is a fundamental oncogenic pathway involved in chemoresistance and proliferation and promotes cell survival when activated. linc01296 and GALNT3 act as resistance “promoters”, while miR-26a acts as a “suppressor”. This regulatory linc01296/miR-26a/GALNT3/MUC1 crosstalk network further activates the PI3K/AKT cascade during the progression of CRC as well as increasing chemoresistance to 5-FU (Fig. 3) [93]. Other examples of mRNA-miRNA-lncRNA crosstalk involved in the chemoresistance of CRC are listed in detail in Table 1.

5.2. GC

GC is the 5th most commonly diagnosed cancer (5.7% of total cases) and 3rd leading cause of cancer death (8.2% of total cases) [1]. Chemotherapy including new adjuvants, adjuvants or advanced treatment options, is the mainly treatment applied [94]. GC patients who show resistance against chemotherapy have a poor five-year-survival rate [95]. A variety of studies on miRNAs, lncRNAs and their crosstalk in GC chemotherapy [96,97] have confirmed that oncogenic lncRNA-D63785 expression is high in GC and that the level is inversely correlated with the expression of miRNA-422a. One of the members of the myocyte enhancer factor 2 (MEF2) transcription factor family, myocyte enhancer factor-2D (MEF2D), also possesses a direct binding site for miRNA-422a. In cancerous cells, MEF2D has a well-established oncogenic role via accelerating metastasis, decreasing apoptosis, and increasing proliferation as well as chemoresistance to different drugs [98,99]. Downregulation of MEF2D by miRNA-422a, the “suppressor” of DOX resistance, is associated with high drug sensitivity. Knockdown of lncRNA-D63785, the “promoter” of DOX resistance, is accompanied by high expression levels of miR-422a and low expression levels of MEF2D, which sensitize GC cells to apoptosis induced by the anticancer drug doxorubicin (DOX). lncRNAs may act as ceRNAs for miRNAs and may stimulate chemoresistance by blocking miRNA-dependent suppression of mRNAs (Fig. 4) [100]. Recently, another study also reported the regulation of the MALAT1/miR-30b/ATG5 ceRNA network in the chemoresistance of GC. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which is highly expressed in GC, sequesters miR-30b by binding to the autophagy-related 5 (ATG5) gene. The upregulation of ATG5 induces autophagy, which in turn leads to CDDP resistance (Fig. 4) [101]. In this network, MALAT1 is a drug resistance "suppressor" and miR-30b is a drug resistance "promoter". We listed the ceRNA networks involved in regulating chemoresistance in other gastric cancers in Table 1. These studies provide promising novel therapeutic targets to overcome resistance against chemotherapeutic drugs used for GC.

5.3. ESCC

ESCC ranks 7th in terms of newly diagnosed cancers (3.2% of total diagnosed cases) and 6th leading as a cause of cancer death (5.3% of total death cases) [1]. Chemotherapy based on the combination of CDDP and 5-FU is widely used chemotherapy for ESCC but over the years there has been less improvement in the survival rate of patients, which is probably due to the presence of an acquired drug resistance [102,103]. As in other GTAs, the lncRNA-miRNA-mRNA regulatory

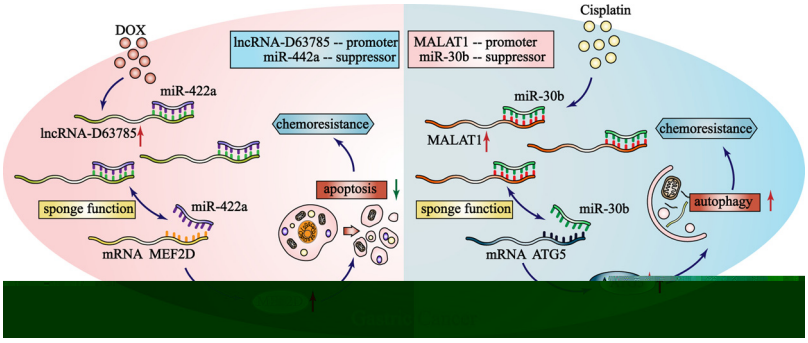

Fig. 4. Dysregulation of the ceRNA network causes chemoresistance in GC. Left) lncRNA-D63785/miR-422a/MAF2D crosstalk decreases the apoptosis of GC cells to promote chemoresistance to DOX. Right) MALAT1/miR-30b/ATG5 crosstalk promotes chemoresistance of CDDP by increasing GC cells autophagy.

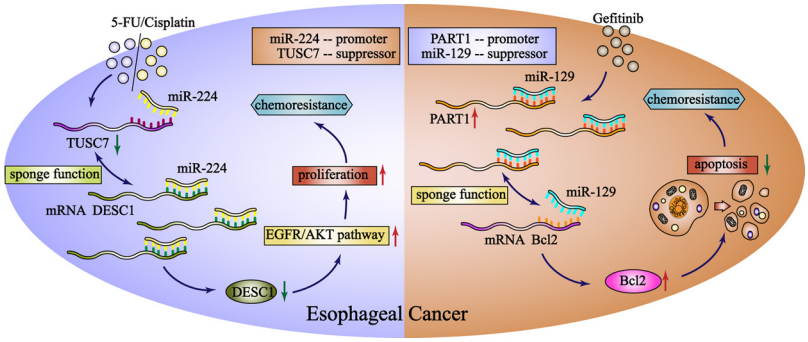

Fig. 5. Dysregulation of the ceRNA network causes chemoresistance in ESCC. Left) The TUSC7/miR-224/DESC1 regulatory network activates the EGFR/AKT pathway, resulting in an increase in proliferation, which causes chemoresistance to 5-FU/CDDP. Right) PART1/miR-129/Bcl2 crosstalk increases the expression of Bcl2, which leads to a chemoresistance to gefitinib by decreasing apoptosis in ESCC cells.

network regulates different pathways involved in ESCC progression. The regulatory network of TUSC7/miR-224/DESC1 is reported to be involved in the chemoresistance of ESCC. The lncRNA tumor suppressor candidate 7 (TUSC7) is downregulated in ESCC and is a potential target of upregulated miR-224. Differentially expressed in squamous cell carcinoma 1 (DESC1) is also downregulated in ESCC and also the target of miR-224 [104]. DESC1 is a tumor suppressor and triggers cell apoptosis by downregulating EGFR/AKT pathway. High expression of drug resistance “suppressor” TUSC7 or inhibition of the drug resistance “promoter” miR-224 reverses cell proliferation as well as resistance to a chemotherapy drug, CDDP, by regulating the DESC1/ EGFR/AKT pathway in ESCC (Fig. 5). Another study also investigated the regulatory function of the ceRNA network and its involvement in drug resistance. According to the study, as the drug resistance “promoter”, the lncRNA prostate androgen-regulated transcript 1 (PART1) is upregulated in gefitinib-resistant cells in comparison to normal ESSC cells. Upregulation of PART1 promotes drug resistance by sponging the drug resistance “suppressor” miR-129 to accelerate the Bcl-2/Bax pathway. The Bcl-2/Bax pathway in turn inhibits apoptotic proteins as well as cell apoptosis, thereby promoting ESCC cells resistance to the anticancer drug, gefitinib (Fig. 5) [105]. The studies presented above identify a complex ceRNA network that is actively involved in the regulation of drug resistance in ESCC. However, the regulation of ceRNA in response to ESCC chemotherapy is not well understood and needs to be explored in future studies.

6. Conclusion and Perspectives

Despite many improvements in the chemotherapeutic treatment of GTAs, resistance to anticancer drugs is still a global challenge to the effectiveness of chemotherapy. Chemoresistance has attracted the attention of researchers due to its significant clinical implications, which has led to the identification of numerous mechanisms responsible for the resistance to chemotherapy. Non-coding RNAs, specifically miRNAs and lncRNAs, are important epigenetic regulators of several mechanisms underlying drug resistance.

Dynamic factors affecting the ceRNA networks including RNA editing, alternative splicing, RNA binding proteins, the secondary structure of RNA transcripts and SNPs, are promising research targets for regulating GTA chemoresistance. Such a network can regulate many biological functions, such as an increase or decrease in the transmission and activity of the drug, the alternation of the target gene, the induction or reduction of the apoptosis of cells and the progression of DNA repair. All these biological functions can change the chemoresistance of cancer cells.

The TME is considered as an emerging target for the cancer chemotherapy due to the varying levels of its influence on carcinogenesis as well as on chemoresitance. Current research is focusing on the multiple reciprocal interactions between the TME, as individual cancer-associated entity, and the ceRNA network, which may be targeted for a successful chemotheraputic response. In GTA cancers, the ceRNA network is widely reported to be involved in the mechanism of chemoresistance. In the ceRNA network, miRNAs or lncRNAs may act as “promoters” or “suppressors” in different conditions to regulate chemoresistance. Thus, the ceRNA network provides a platform to overcome chemoresistance and improve the survival of cancer patients.

Treatment strategies of “replacement” or ‘inhibition” can be based on the down- or up-regulation of miRNAs in GTAs, which may improve the outcome of anticancer drug treatments. Currently, several transcriptomic studies are geared towards investigating the dysregulation of miRNA and lncRNA in GTAs but still need to investigate the ceRNA network and its involvement in chemoresistance. The regulation of this dysregulation by the use of non-coding RNA-based drugs is one of the fundamental objectives in overcoming chemoresistance. The field of non-coding RNA therapeutics is still in its infancy and needs to explore the fine association of lncRNAs, miRNAs and mRNAs in response to chemotherapeutic drugs in order to provide promising opportunities for effective treatment strategies to overcome anticancer drug resistance. Moreover, studies should explore the use of ceRNA network in predicting possible treatment and resistance responses, which will be helpful to obtain individualized chemotherapeutic treatment as well as to improve patient outcomes and survival.

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Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Khadija Raziq: Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Mengdi Cai:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Kexian Dong:** Conceptualization, Visualization. **Ping Wang:** Conceptualization, Validation. **Justice Afrifa:** Conceptualization. **Songbin Fu:** Conceptualization, Funding acquisition.

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