



# Non-Coding RNAs and Resistance to Anticancer Drugs in Gastrointestinal Tumors

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Non-coding RNAs are important regulators of gene expression and transcription. It is well established that impaired non-coding RNA expression especially the one of long non-coding RNAs and microRNAs is involved in a number of pathological conditions including cancer. Non-coding RNAs are responsible for the development of resistance to anticancer treatments as they regulate drug resistance-related genes, affect intracellular drug concentrations, induce alternative signaling pathways, alter drug efficiency *via* blocking cell cycle regulation, and DNA damage response. Furthermore, they can prevent therapeutic-induced cell death and promote epithelial–mesenchymal transition (EMT) and elicit non-cell autonomous mechanisms of resistance. In this review, we summarize the role of non-coding RNAs for different mechanisms resulting in drug resistance (e.g., drug transport, drug metabolism, cell cycle regulation, regulation of apoptotic pathways, cancer stem cells, and EMT) in the context of gastrointestinal cancers.

**Keywords:** non-coding RNA, lncRNA, microRNA, anticancer drugs, gastrointestinal tumor, cancer therapy, resistance

## INTRODUCTION

Gastrointestinal (GI) cancer encompasses a heterogeneous group of tumors that affect the digestive tract system (1). These include cancers of the esophagus, stomach, gallbladder, liver and biliary tract, pancreas, small intestine, colon, rectum, and anus. GI cancer is the most common form of cancer responsible for nearly 25% of all new cancer diagnosis and responsible for most of cancer-related death (around 30% of all cancer-related death) worldwide (2, 3).

Chemotherapy is, alongside with surgery and radiation therapy, one of the main treatments for cancer (4–12). Many chemotherapeutic agents have successfully prolonged overall and progression-free survival of GI cancer patients (13–17). In addition, a better understanding of the biology and mechanism underpinning GI cancer initiation and progression is leading to more personalized treatments. Indeed, identification of well-defined molecular subtypes and/or molecular profiling of somatic mutations offer the opportunity to further optimize the efficacy of treatments through tailored approaches (18–21).

Despite major improvements in the management of GI cancer patients, resistance to therapies arises almost inevitably at some point during the treatment and chemoresistance is one of the main challenges in cancer therapy (22). Drug resistance can be caused by gene mutations, abnormal DNA repair, alteration in cell cycle regulation, cell death inhibition (mostly caused by deregulated apoptotic signaling pathways), reduced drug efficacy, and enhanced drug clearance (22, 23). Furthermore, the epithelial–mesenchymal transition (EMT) process and the presence of tumor stem cells have

been identified as causes of drug resistance (24–27). The complex molecular mechanisms of chemoresistance have not been fully elucidated yet and a better understanding of drivers of primary and secondary resistance to chemotherapy will likely result into improved patients' survival. Increasing evidence points toward the role of non-coding RNAs as a central hub for treatment resistance. Therefore, this review outlines the role of non-coding RNAs for the different drug resistance mechanisms involved in GI cancer therapy failure. **Table 1** summarized the non-coding RNAs discussed in this review; and in **Figures 1–7**, the role for

each of these non-coding RNAs in the context of the different GI tumors is illustrated.

## NON-CODING RNAs

In human tissues, the amount of non-coding RNAs is more than three times higher compared to the amount of protein-coding RNAs (189). Non-coding RNAs are a large family that includes more than 16 categories of long and short RNA molecules (**Table 2**); among them transfer RNAs (tRNAs), ribosomal RNAs

**TABLE 1** | Overview about non-coding RNAs involved in resistance to anticancer drugs in gastrointestinal tumors.

Non-coding RNA	GI cancer type	Causing drug resistance via	Reference
lncRNA AK022798	Gastric cancer	Increasing the expression of <i>ABCB1</i> gene	(28)
lncRNA ANRIL	Gastric cancer	Increasing the expression of <i>MDR1</i> gene	(29, 30)
lncRNA ARA	Liver cancer	Reduced G2/M cell-cycle arrest; reduced apoptosis rate; deregulation of MAPK-pathway	(31, 32)
lncRNA-ATB	Liver cancer	Increased expression of ZEB1 and ZEB2; induced EMT	(33)
lncRNA CCAL	Colorectal cancer	Increasing the expression of <i>ABCB1</i> gene; increased activity of Wnt/ $\beta$ -catenin pathway	(34)
lncRNA H19	Liver cancer esophageal cancer	Upregulation of membrane glycoprotein p95; elevating the expression of <i>MDR1</i> gene by increasing promoter methylation; increasing telomere length	(35–37)
lncRNA HOTAIR	Liver cancer Colorectal cancer Pancreatic cancer Gi stromal tumor	Increased expression of PRC2 complex members; genome-wide changes in transcription process due to epigenetic chromatin silencing; downregulation of p21(WAF/CIP1); repression of G1/S cell-cycle arrest; increased proliferation rate; reduced DNA-damage response	(38–41)
lncRNA HOTAIR	Colon cancer Pancreatic cancer Gastric cancer esophageal cancer	Transformation of stem cells into cancer stem cells due to activation of <i>OCT4</i> , <i>RNF51</i> , <i>CD44</i> , and <i>CD133</i> gene expression; increased activity of Wnt/ $\beta$ -catenin pathway; modulation of chromatin organization leads to reduced efficiency of the mismatch repair system; increased MSI; reduced apoptosis rate; inhibition of the expression of miR-126 and activating the PI3K-AKT-mTOR pathway (in gastric cancer)	(42–48)
lncRNA HOTTIP	Pancreatic cancer	Increased expression of transcription factor HOX13; cell cycle deregulation	(49, 50)
lncRNA HULC	Liver cancer	Increased activity of Wnt- $\beta$ -catenin; increased expression of USP22 and SIRT1; reduced expression of miR-6825-5p, miR-6845-5p, miR-6886-3p; increased autophagy pathway	(51)
lncRNA HULC	Gastric cancer	Induced EMT; suppressed apoptosis	(52, 53)
lncRNA LEIGG	Gastric cancer	Induced EMT	(54, 55)
lncRNA linc-ROR	Pancreatic cancer	Inhibition of p53; inhibition of the expression of miR-200 family; increased expression of the transcription factor ZEB1; induced EMT	(56, 57)
lncRNA linc-ROR	Liver cancer	Preventing the binding of miR-145 to pluripotent factors OCT-4, NANOG, and SOX2 resulting in increased expression of these transcription factors necessary for sustain stem cell character	(58, 59)
lncRNA LOC285194	esophageal cancer	Cell-cycle deregulation; blocking non-apoptotic cell death pathway	(60)
lncRNA MALAT-1	esophageal tumor	Binds miR-107 and miR-217; reduced activity of the ATM-CHK2 signaling pathway; reduced cell-cycle arrest and cell death as response to DNA damage; increased expression of transcription factor B-Myb	(61–63)
lncRNA MALAT-1	Pancreatic cancer	Increased expression of cancer stem cell marker CD133; increased expression of pluripotent factors OCT4, NANOG, and SOX2; induced EMT; repression of G2/M cell-cycle arrest; reduced apoptosis rate	(64–66)
lncRNA MALAT-1	Gastric cancer	Sequestering of miR-23b-3p; increased expression of ATG12; increased autophagy	(67)
lncRNA MIR100HG	Colon cancer	Increased activity of Wnt- $\beta$ -catenin pathway	(68)
lncRNA MRUL	Gastric cancer	Increasing the expression of <i>MDR1</i> gene	(69)
lncRNA PANDAR	Gastric cancer Colorectal cancer Hepatocellular cancer cholangiocarcinoma	Interacts with the transcription factor NF-YA resulting in reduced translation of proapoptotic genes—leading to reduced apoptosis rate and increased proliferation	(70–74)
lncRNA PVT1	Gastric cancer esophageal cancer Pancreatic cancer Colon cancer Liver cancer	Induced EMT	(75–77)

(Continued)

TABLE 1 | Continued

Non-coding RNA	GI cancer type	Causing drug resistance via	Reference
lncRNA PVT-1	Gastric cancer	Increasing the expression of <i>MDR1</i> gene	(29, 30)
lncRNA TUC338	Hepatocellular cancer	Inhibiting the RASAL-1 pathway	(78)
lncRNA TUG1	esophageal cancer Gastric cancer Colorectal cancer Hepatocellular cancer cholangiocarcinoma	Increasing the expression of <i>Bc-2</i> gene; reducing the expression of cyclin-dependent protein kinase, caspase-3, caspase-9, and Bax; decreasing G0/G1 arrest during cell cycle; reducing apoptosis rate; inducing EMT	(79–85)
lncRNA UCA1 (identical with lncRNA CDUR)	Liver cancer Colorectal cancer Pancreatic cancer Gastric cancer esophageal cancer	Sequestering microRNAs (miR-216b in liver cancer; miR-204-5p in colorectal and esophageal cancer; miR-27 in gastric cancer); increase expression of lncRNAs (HULC; H19); increased activity of Wnt- $\beta$ -catenin pathway; increased activity of PI3K-AKT-mTOR pathway; increased phosphorylation of tumor suppressor retinoblastoma; increased expression of c-myc; increased cell-cycle progression; increased expression of antiapoptotic protein Bcl-2; reduced expression of PARP (in gastric cancer); reduced apoptosis rate. In liver cancer, additional effects: transformation of stem cells into cancer stem cells due to increased c-myc expression; increasing telomere length	(35, 86–96)
lncRNA URHC	Liver cancer	Reduced expression of the tumor suppressor ZAK; increased proliferation rate; reduced apoptosis rate	(97)
lncRNA-34a	Colon cancer	Increased activity of Wnt- $\beta$ -catenin pathway; increased activity of NOTCH pathway; increasing the self-renewal of cancer stem cells	(98, 99)
miR let-7 family	Pancreatic cancer	Induced EMT	(100)
miR let-7a	Pancreatic tumors	Increased expression of RRM2	(101)
miR let-7g	esophageal cancer	Increased expression of ABCC10	(102)
miR let-7i	esophageal cancer	Increased expression of ABCC10	(102)
miR-100	Colon cancer	Increased activity of Wnt- $\beta$ -catenin pathway	(68)
miR-101	Liver cancer	Increased expression of EZH2; increased activity of Wnt- $\beta$ -catenin pathway; increased expression of Mcl-1; reduced apoptosis rate	(103–105)
miR-10b	Colorectal cancer	Increased expression of antiapoptotic protein Bim	(106)
miR-103/107	Gastric cancer	Reduced expression of tumor-suppressor caveolin-1; activation of Ras-p42/p44 MAP pathway; reduced apoptosis rate	(107–109)
miR-106a	Gastric cancer	Reduced expression of FAS; reduced apoptosis rate	(110, 111)
miR-1182	Gastric cancer	Increased expression of hTERT	(112)
miR-122	Liver cancer	Increased expression of ABC proteins; increased expression of cyclin G1; reduced G2/M cell-cycle arrest; reduced DNA repair; reduced apoptosis rate	(113, 114)
miR-124	Pancreatic cancer Liver cancer	Reduced expression of SLC16A1	(115)
miR-125b	Colon cancer	Increased activity of Wnt- $\beta$ -catenin pathway	(68)
miR-1246	Pancreatic cancer	Reduced expression of cyclin-G2; deregulated cell-cycle	(116)
miR-129	Colorectal cancer	Increased expression of antiapoptotic protein Bcl-2	(117)
miR-1291	Pancreatic cancer	Increased expression of ABCC1	(118)
miR-130b	Liver cancer	Reduce expression of tumor protein 53-induced nuclear protein 1	(119)
miR-1307	Pancreatic cancer	Reduced apoptosis rate	(120)
miR-133a	esophageal cancer	Increased expression of GSTP1	(121)
miR-145	Colon carcinoma	Increased expression of ABCB1	(122)
miR-147	Colon cancer	Induced EMT; increased phosphorylation of AKT; increased activity of PI3K-AKT-mtor pathway; increased activity of TGF- $\beta$ pathway	(123)
miR-155	Colorectal cancer	Inhibition of MSH2, MSH6, and MLH1	(124)
miR-15b	Gastric cancer	Increased expression of antiapoptotic protein Bcl-2	(125)
miR-16	Gastric cancer	Increased expression of antiapoptotic protein Bcl-2	(125)
miR-17-5p	Colorectal cancer	Reduced expression of PTEN expression; activation of AKT-mtor pathways	(126)
miR-17-5p	Pancreatic cancer	Reduced expression of BIM	(127)
miR-1915	Colon cancer	Increased expression of BCL-2	(128)
miR-192	Colon cancer	Reduced expression of thymidylate synthase; altered cell-cycle control at multiple levels; prevent progression into the S-phase	(129)
miR-193b	Hepatocellular cancer	Increased expression of Mcl-1	(130)
miR-195	Colorectal cancer	Increased expression of antiapoptotic protein Bcl-2L2	(131)

(Continued)

TABLE 1 | Continued

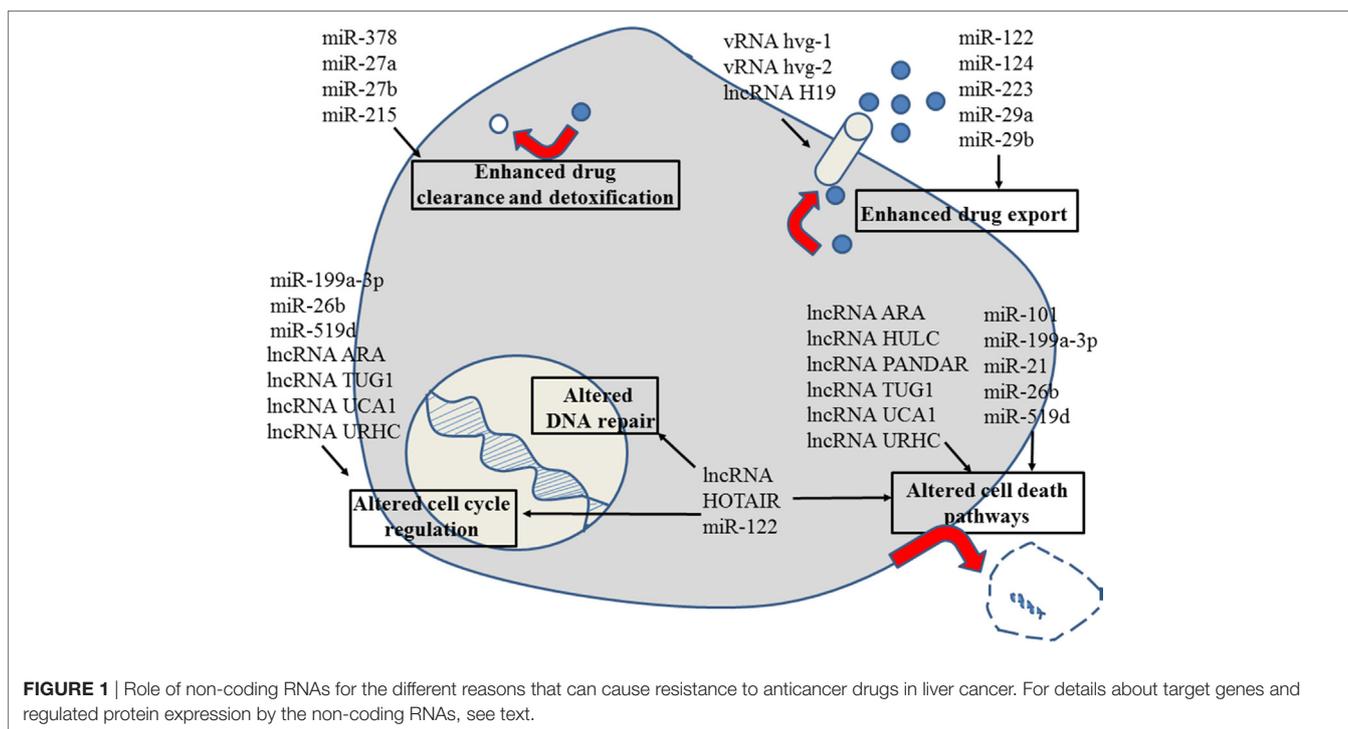
Non-coding RNA	GI cancer type	Causing drug resistance via	Reference
miR-199a-3p	Liver cancer	Reduced G1/S cell-cycle arrest; increased expression of mtor and c-Met; reduced apoptosis rate	(132, 133)
miR-19a	Gastric cancer	Reduced expression of PTEN expression; activation of AKT-mtor pathways	(134)
miR-19b	Gastric cancer	Reduced expression of PTEN expression; activation of AKT-mtor pathways	(134)
miR-200a	Pancreatic cancer	Induced EMT	(100)
miR-200b	Pancreatic cancer	Induced EMT	(100)
miR-200c	Pancreatic cancer	Induced EMT	(100, 135)
miR-203	Colorectal cancer	Reduced expression of ATM; impaired DNA repair; reduced apoptosis rate	(136)
miR-205	Pancreatic cancer	Increased expression of pluripotent factors OKT3, OKT8, and CD44	(137)
miR-21	Colorectal cancer	Inhibition of MSH2 and MSH6; reduced G2/M cell-cycle arrest; reduced apoptosis rate; increasing the number of undifferentiated cancer stem cells	(138, 139)
miR-21	Pancreatic cancer	Reduced cell-cycle arrest; reduced expression of PTEN; activation of AKT-mtor pathway; increased expression of antiapoptotic protein Bcl-2; increased cell proliferation; reduced apoptosis rate	(140, 141)
miR-21	Liver cancer Gastric cancer	Reduced expression of PTEN expression; activation of AKT-mtor pathways	(142–144)
Synergistic action of miR-21	Pancreatic cancer	Reduced expression of the tumor suppressors PDCD4, BTG2, and NEDD4L; deregulated cell-cycle; reduced apoptosis rate	(145, 146)
miR-23a			
miR-27a			
miR-211	Pancreatic tumors	Increased expression of RRM2	(147)
miR-215	Liver cancer	Reduced expression of dihydrofolate reductase; reduced expression of thymidylate synthase	(148)
miR-215	Colon cancer	Reduced expression of thymidylate synthase; altered cell-cycle control at multiple levels; prevent progression into the S-phase	(129)
miR-215	Gastric cancer	Reduced expression of retinoblastoma 1; altered cell-cycle control	(149, 150)
miR-22	P53-mutated colon cancer	Reduced expression of PTEN expression; activation of AKT-mtor pathways	
miR-221	esophageal cancer	Reduced expression of DDK2; activation of Wnt/ $\beta$ -catenin pathway; induced EMT	(151, 152)
miR-223	Liver cancer	Increased expression of ABCB1	
miR-223	Pancreatic cancer	Induced EMT	(153)
miR-223	Gastric cancer	Reduced expression of FBXW7; altered cell-cycle control	(154)
miR-224	Colon cancer	Induced EMT; increased phosphorylation of AKT und ERK; increased activity of PI3K-AKT-mtor pathway; increased activity of ERK pathway; activation of NF- $\kappa$ B; and EGFR dependent pathways	(155)
miR-23a	Microsatellite instable colon cancer	Increased expression of ABCF1	(156)
miR-25	Gastric cancer	Reduced expression of FOXO3a, ERBB2, and FBXW7; cell-cycle deregulation; reduced apoptosis rate	(157–160)
miR-26b	Liver cancer	Increased activation of NF- $\kappa$ B	(161, 162)
miR-27a	Liver cancer	Reduced expression of dihydropyrimidine dehydrogenase	(163)
miR-27b	Liver cancer	Increased expression of CYP1B1; reduced expression of dihydropyrimidine dehydrogenase	(163, 164)
miR-27b	Pancreatic cancer	Reduced expression of CYP3A4—resulting in cyclophosphamide resistance due to missing drug activation	(165)
miR-297	Colorectal cancer	Increased expression of ABCC2	(166)
miR-29a	Pancreatic cancer Liver cancer	Reduced expression of SLC16A1	(115)
miR-29b	Pancreatic cancer Liver cancer	Reduced expression of SLC16A1	(115)
miR-31	Colorectal cancer	Cell-cycle deregulation; reduced apoptosis rate	(167, 168)
miR-320	Colon cancer	Increased expression of SOX4; inhibition of p53 mediated apoptosis; reduced expression of FOXM1 and FOXQ1; cell-cycle deregulation	(169, 170)
miR-338-3p	p53 mutant colorectal cancer	Reduced expression of mtor; increased autophagy; and reduced apoptosis rate	(171)
miR-34a	Colon cancer	Increased expression of antiapoptotic protein Bcl-2	(172)
miR-365	Colon cancer	Increased expression of antiapoptotic protein Bcl-2	(173)
miR-374b	Pancreatic cancer	Increased ATP7A expression	(174)
miR-378	Liver cancer	Increased expression of CYP2E1	(175)

(Continued)

**TABLE 1** | Continued

Non-coding RNA	GI cancer type	Causing drug resistance via	Reference
miR-409-3p	Colon cancer	Increased expression of Beclin-1; increased autophagy pathway	(176)
miR-451	Colon cancer	Increasing the self-renewal of cancer stem cells; increased expression of ABCB1	(177)
miR-494	Colon cancer	Reduced expression of dihydropyrimidine dehydrogenase	(178)
miR-503-5p	Colorectal cancer	Reduced expression of apoptotic protein PUMA	(179)
miR-508-5p	Gastric cancer	Increased expression of ABCB1; increased expression of transcription factor ZNRD1	(180)
miR-519d	Liver cancer	Reduced expression of G1-checkpoint CDK inhibitor p21; reduced apoptosis rate	(181)
miR-522	Colon cancer	Increased expression of ABCB5	(182)
miR-92b	Colon cancer	Reduced expression of SLC15A and SLC15A1	(183)
miR-939	Gastric cancer	Increased expression of SLC34A2; activation of Ras/MEK/ERK pathway	(184)
miR-96	Colorectal cancer	Reduced expression of antiapoptotic proteins XIAP and UBE2N	(185)
svRNAb	All GI tumors	Reduced expression of CYP3A4	(186)
vRNA hvg-1	All GI tumors	Transporting drugs away from the target and drug sequestration	(187, 188)
vRNA hvg-2	All GI tumors	Transporting drugs away from the target and drug sequestration	(187, 188)

GI, gastrointestinal; vRNA, vault RNA; lncRNA, long non-coding RNA; miR, microRNA; EMT, epithelial–mesenchymal transition.

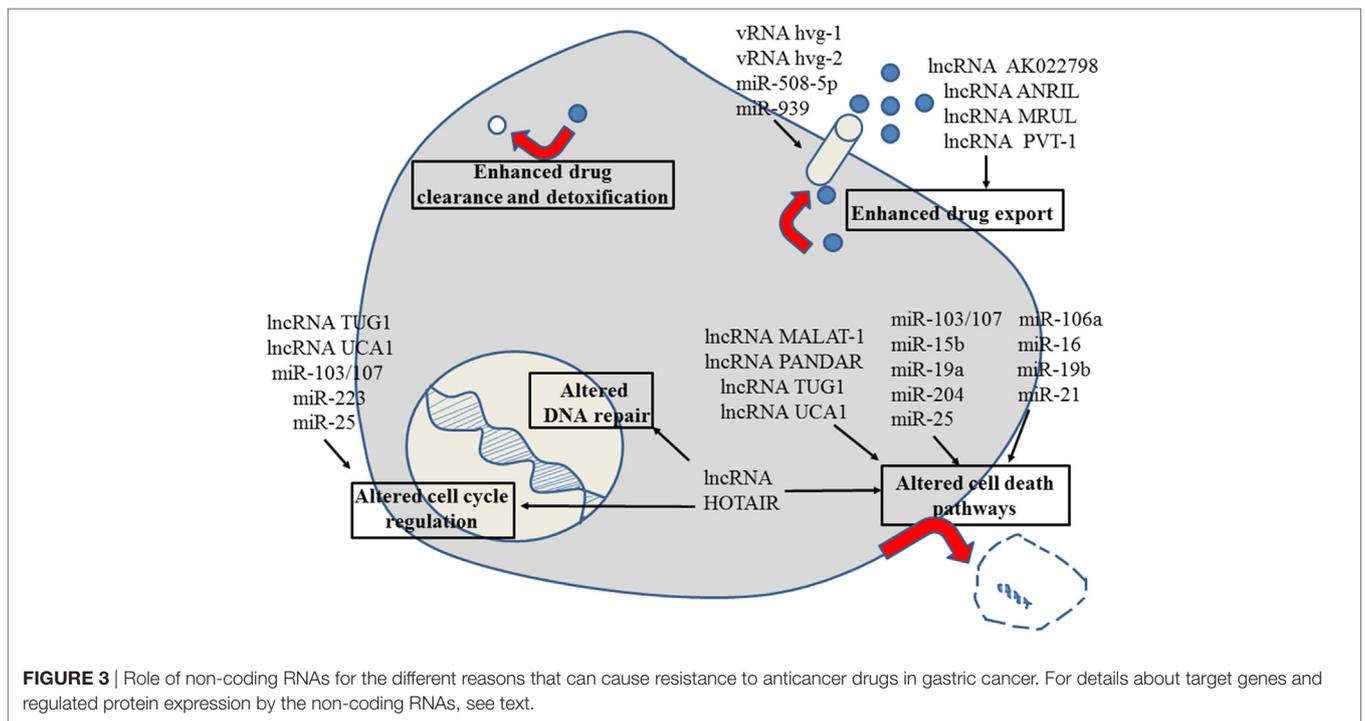
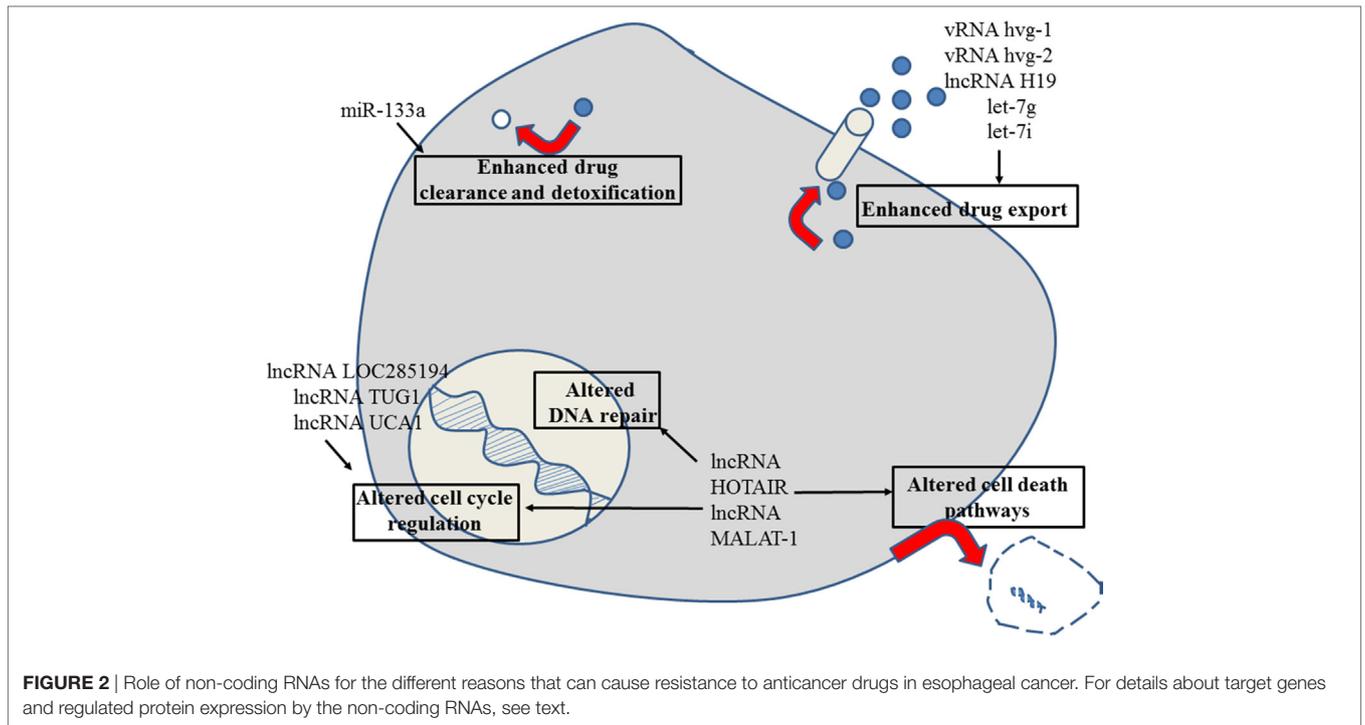


**FIGURE 1** | Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in liver cancer. For details about target genes and regulated protein expression by the non-coding RNAs, see text.

(rRNAs), small nucleolar RNAs (snoRNAs), endogenous small interfering RNAs (endo-siRNAs), sno-derived RNAs (sdrRNAs), transcription initiation RNAs (tiRNAs), miRNA-offset-RNAs (moRNAs), circular RNAs (circRNAs), vault RNAs (vRNAs), microRNAs, small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), extracellular RNAs (exRNAs), piwi-interacting RNAs (piRNAs), small Cajal body RNAs (scaRNAs), long intergenic non-coding RNAs (lincRNAs), and long non-coding RNAs (lncRNAs), all of which are not coding for known proteins (190–211).

Long non-coding RNAs (lncRNAs) and microRNAs are the most studied non-coding RNAs playing a role in anticancer drug resistance and will be covered in this review.

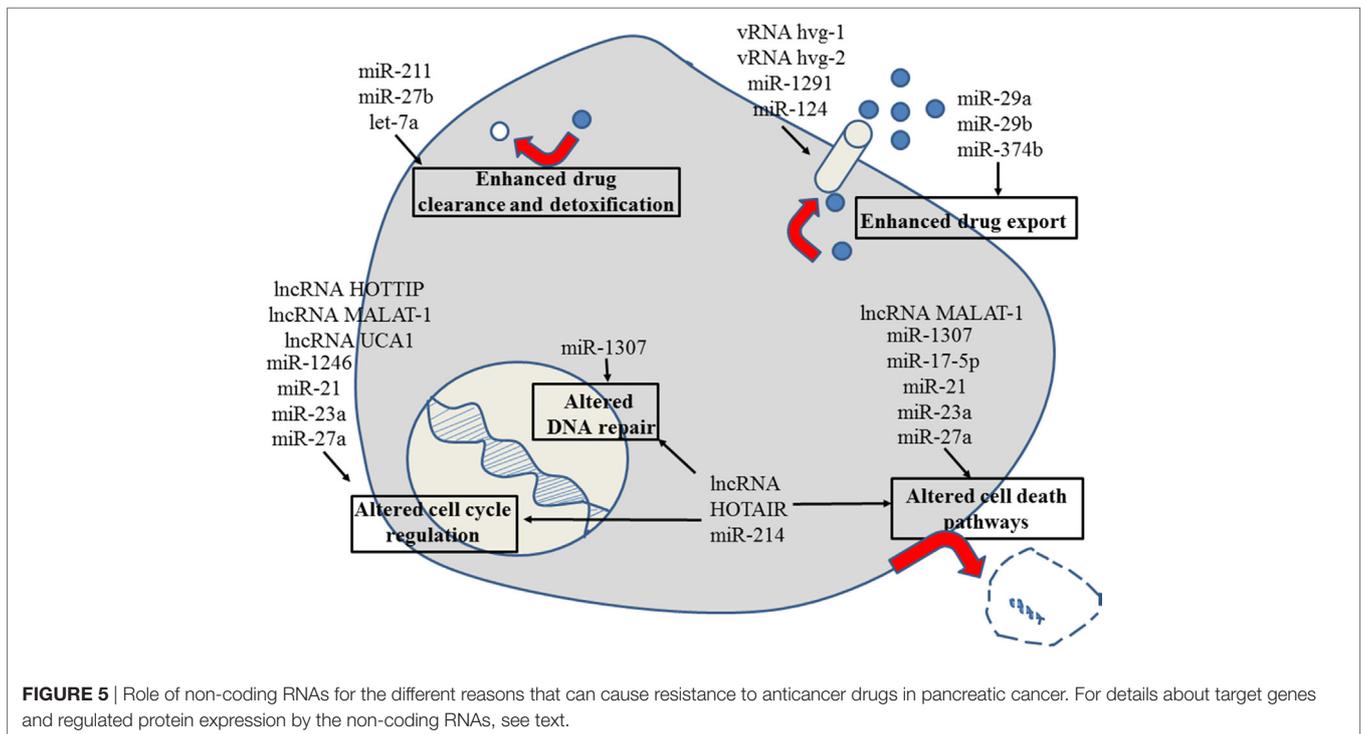
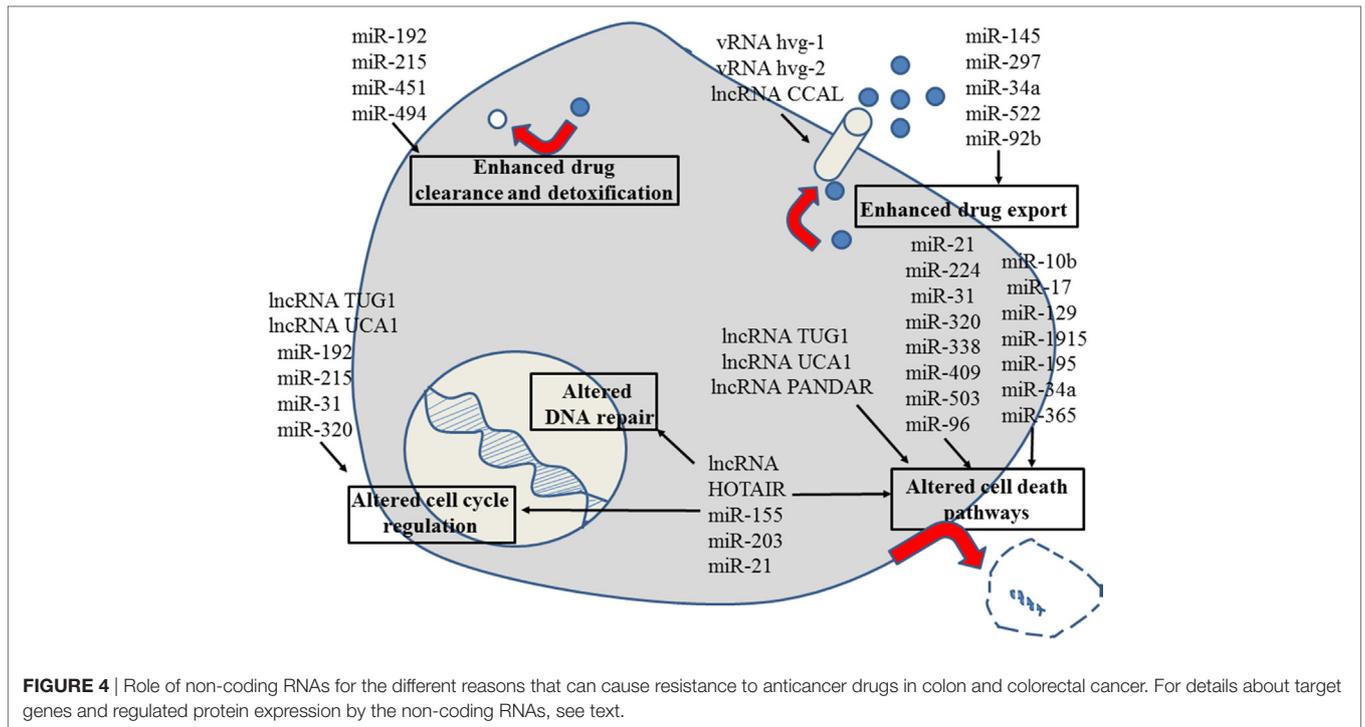
lncRNAs are composed of more than 200 nucleotides. They are important regulators during development and pathological processes (212–216). lncRNAs are pivotal in regulating gene expression by binding to chromatin regulatory proteins and they are able to alter chromatin modification as well as transcriptional or posttranscriptional gene regulation by interacting with other RNAs and proteins (217–219). Recently, a crosstalk and strong linkage between lncRNA and microRNAs has been identified (220). It has been shown that lncRNA stability can be reduced by interaction with specific microRNAs and, *vice versa*, lncRNAs act as microRNA decoys sequestering microRNAs from the intracellular cytosol and leading to reexpression of microRNA target genes (220). Furthermore, lncRNAs can promote gene expression



by competing with microRNAs for specific binding sites in the non-coding regions of mRNAs and prevent the transcriptional repression caused by microRNAs (220). Interestingly some lncRNAs can be processed into microRNAs (220) suggesting a plastic interaction among different classes of non-coding RNAs.

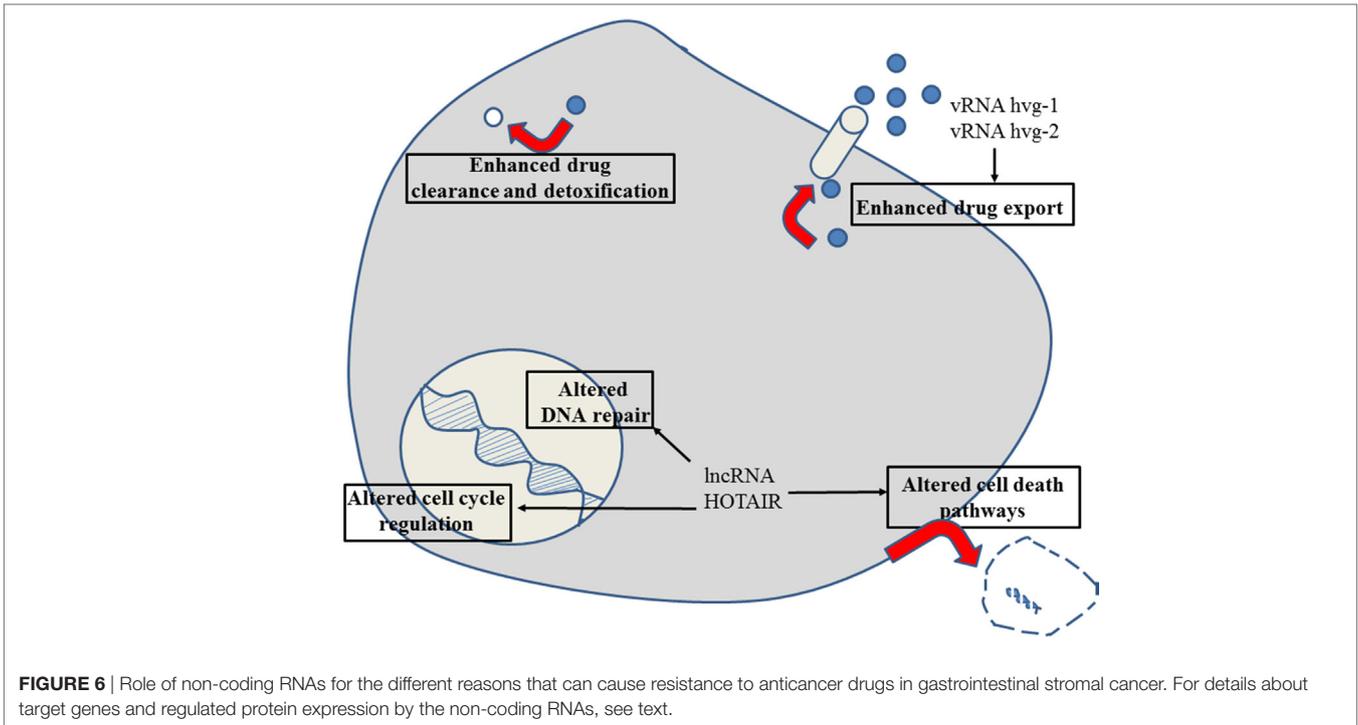
MicroRNAs are short RNA transcripts of 18–24 nucleotides. They are responsible for fine tuning cell homeostasis by

controlling gene expression at posttranscriptional level (221–223). Due to the fact that each microRNAs can have several target mRNAs, the interaction of one microRNA with various target mRNAs results in direct deregulation of different target proteins acting simultaneously in regulation of diverse cellular pathways (224, 225). Therefore, variation in microRNA expression can result in reduced mRNA levels ultimately resulting in changes

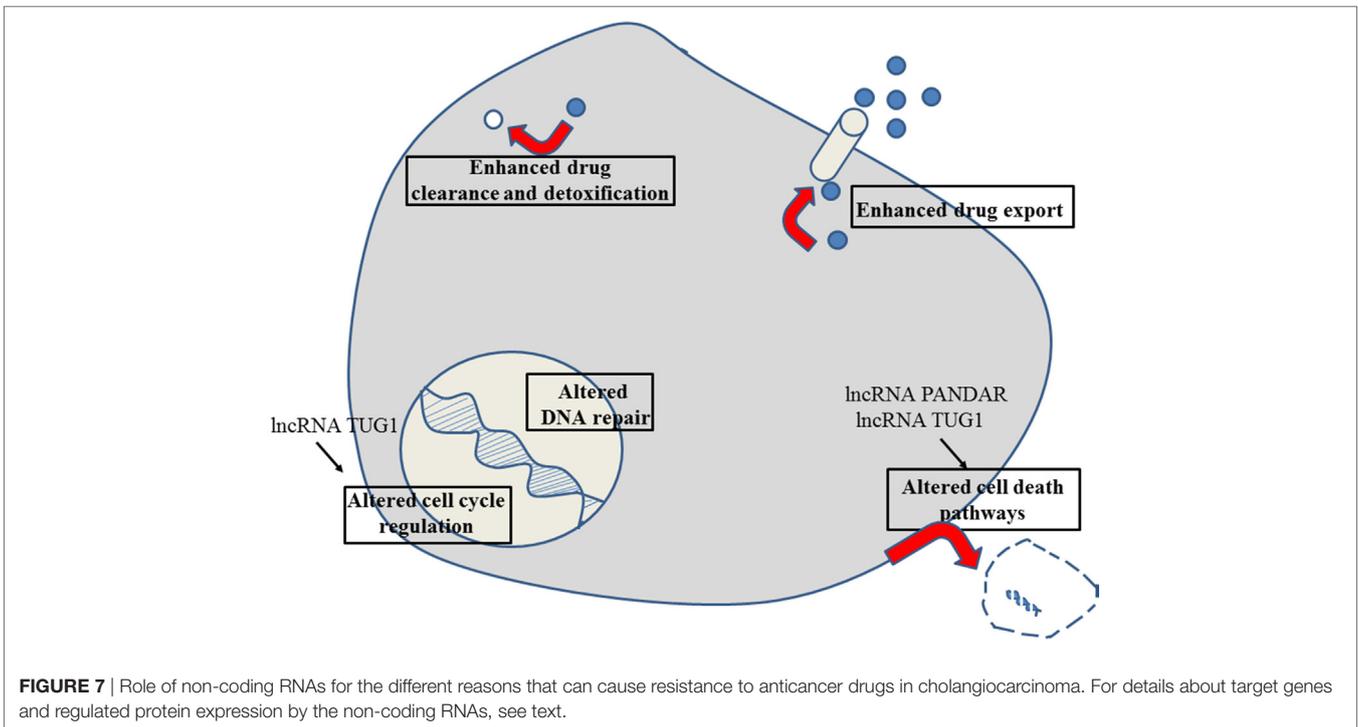


in protein levels within the cell (225, 226). MicroRNAs expression patterns are tissue specific (227) and often define the physiological status of the cell (228). Strong clinical and preclinical evidence suggests that microRNA aberrant expression plays a role in several diseases including cancer, infectious,

neurodegenerative, and immune-related diseases (229–240). Analysis of microRNA expression patterns represents a promising tool for cancer diagnosis, prognosis and treatment prediction. MicroRNAs have been extensively studied in monitoring treatment resistance in consideration of their high stability in



**FIGURE 6** | Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in gastrointestinal stromal cancer. For details about target genes and regulated protein expression by the non-coding RNAs, see text.



**FIGURE 7** | Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in cholangiocarcinoma. For details about target genes and regulated protein expression by the non-coding RNAs, see text.

tissues and body fluids. In blood, microRNAs are included in RNA-binding multiprotein complexes and/or exosomes and their short length makes microRNAs less prone to degradation and improves their stability under different sample storage conditions in blood (224, 230, 236, 240).

## GENERAL PRINCIPLES OF DRUG RESISTANCE

Drug resistance is classified into intrinsic and acquired. Primary drug resistance is pre-existing and renders cancer cells immune

**TABLE 2** | Overview about the different categories of non-coding RNA molecules.

Name	Biological role
Circular RNA (circRNA)	Involved in forming RNA-protein complex that regulate gene transcription; involved in regulating gene expression at posttranscriptional level by acting as miRNA sponge
Endogenous small interfering RNA (endo-siRNA)	Involved in repression of transposable elements, chromatin organization as well as gene regulation at transcriptional and posttranscriptional level
Extracellular RNA (exRNA)	Involved in intercellular communication and cell regulation
Long intergenic non-coding RNA (lincRNA)	Involved in gene expression <i>via</i> directing chromatin-modification complexes to specific target regions; lincRNAs located in the cytoplasm function as scaffold to bring together proteins and other RNA categories (especially mRNAs and miRNAs)
Long non-coding RNA (lncRNA)	Involved in regulation of gene expression <i>via</i> binding to chromatin regulatory proteins; involved in regulating gene expression at posttranscriptional level by acting as microRNA decoys; some lncRNAs are processed into microRNAs
MicroRNA	Involved in fine tuning cell homeostasis by controlling gene expression at posttranscriptional level
miRNA-offset-RNA (moRNA)	Unknown
piwi-interacting RNA (piRNA)	Involved in maintain germline integrity by repressing transposable elements; involved in mRNA deadenylation
Ribosomal RNA (rRNA)	Component of the ribosomes; involved in protein synthesis
Small Cajal body RNA (scaRNA)	Component of the Cajal bodies; involved in the biogenesis of small nuclear ribonucleoproteins and by this influence splicing of pre-mRNAs
Small interfering RNA (siRNA)	Involved in RNA interference pathway as part of antiviral defense
Small nuclear RNA (snRNA)	Component of the spliceosome; involved in splicing of pre-mRNAs during posttranscriptional modifications
Small nucleolar RNA (snoRNA)	Component of the Cajal bodies; involved in modification and processing of snRNA, rRNA and tRNA precursors as well as in mRNA editing
sno-derived RNA (sdRNA)	Component of the Cajal bodies; involved in alternative splicing of mRNAs; some sdRNAs control gene expression at posttranscriptional level
Transcription initiation RNA (tiRNA)	Involved in regulation of RNA polymerase II dependent transcription
Transfer RNA (tRNA)	Involved in transporting amino acids to the ribosomes during translation
Vault RNA (vRNA)	Component of the vaults (large ribonucleoprotein complexes in cytoplasm); unknown function

against the therapy from the very beginning. In contrast, acquired (secondary) drug resistance develops during therapy due to adaptive processes of the tumor (22, 241–244). Different mechanisms are involved in primary and acquired drug resistance and relate to non-coding RNAs dysregulation.

## Deregulation of Proteins Involved in Drug Metabolism

One reason for drug resistance can be found on the level of drug transport. Reduced influx or increased efflux of chemotherapeutics result in lower intracellular drug concentrations and promotes therapy failure (241). Altered drug metabolism is another possible cause for drug resistance. Drug metabolism is a complex pathway composed of multiple proteins for detoxification of foreign compounds (e.g., chemotherapeutics) normally neither produced nor present in a cell (245). This pathway can be subdivided into modification (phase I reaction), conjugation (phase II reaction), and excretion (phase III reaction) (246). Several drug-metabolizing enzymes, especially members of the cytochrome P450 family, together with drug transporters increase the polarity of the drugs during phase I (247, 248). In the following phase II, the polarity of the drugs is further increased by conjugation reactions (249, 250). Finally, in phase III the resulting drug metabolites are exported by transmembrane transporter like ATP-binding cassette (ABC) proteins and solute carrier (SLC) transport proteins (251–254).

The vaults are known to contribute to drug resistance by transporting drugs away from their intracellular targets and vaults are involved in drug sequestration (187). The vRNAs hvg-1 and hvg-2 that are present in the vaults (Table 2) interact with drugs *via* specific binding sites (188). In agreement with their role in regard to drug resistance, the number of vaults is increased in cancer patients who developed resistance under chemotherapy (187). In addition, the vRNAs are producing several small RNAs among them is svRNAb which downregulates the key enzyme in drug metabolism CYP3A4 and accounts so for multidrug resistance in GI cancers (186).

Furthermore, lncRNA H19 was identified as another non-coding RNA involved in drug resistance. The oncogenic potential of lncRNA H19 was demonstrated in different tumor types (e.g., liver and esophageal cancer) and overexpression of lncRNA H19 was observed in parallel with upregulation of the membrane glycoprotein p95 in multidrug-resistant tumors (36, 37). In liver tumor cells, resistant to doxorubicin, etoposide, paclitaxel, and vincristine lncRNA H19 expression was increased (36). lncRNA H19 participates in the regulation of *MDR1* gene (also known as *ABCB1* gene) expression and modulates the drug transport out of the cell (36). *In vitro* models of hepatocellular carcinoma suggest that lncRNA H19 can alter *MDR1* promoter methylation and, in doing so, increases the transcription of P-glycoprotein (36).

Similarly, in gastric cancer, MDR-related and upregulated lncRNA (lncRNA MRUL) acts as an enhancer for transcription of P-glycoprotein (*MDR1*) (69) increasing the number of

transmembrane transporters on the tumor cell membrane and fosters the drug export (69). As we described above, different non-coding RNAs can merge onto the same pathway: this is the case of lncRNA AK022798 whose expression is induced by NOTCH-1 overexpression during gastric cancer progression (28). LncRNA AK022798 in turn upregulates the expression of P-glycoprotein and is responsible for increased cisplatin resistance in gastric cancer patients (28). Similarly, in cisplatin and 5-fluorouracil-resistant gastric cancer patients the expression of lncRNA plasmacytoma variant translocation 1 (PVT-1) and lncRNA ANRIL (antisense to CDKN2B locus) are also increased and these non-coding RNAs promote MDR1 upregulation and drug resistance (29, 30).

Non-coding RNA dysregulation is tissue specific, indeed Wnt- $\beta$ -catenin pathway activation triggers the expression of a different lncRNA, colorectal cancer-associated lncRNA (CCAL). The effect on phenotype is the same as in other cancers given CCAL in turn upregulates P-glycoprotein expression and causing chemotherapy resistance (34).

Additional to the regulation *via* lncRNAs ABC transporter expression levels are also controlled by miRNAs (255, 256).

In colon cancer, P-glycoprotein expression was found to be directly deregulated at posttranscriptional level by binding of miR-145 to the 3'-UTR of the *MDR1* gene transcript (122). Downregulation of miR-145 results in increased ABCB1 protein level (122). Analogously miR-297 binds to the 3'-UTR of ABCC2 mRNA and suppresses the expression of ABCC2 transporter (166). In chemoresistant colorectal carcinoma, miR-297 is often downregulated and consequently ABCC2 is expressed on a higher level compared to the surrounding colon tissue (166). Interestingly, *in vitro* and *in vivo* models suggest that resistance to vincristine and oxaliplatin could be overcome by restoring miR-297 expression in therapy-resistant cells (166). Virtually expression of all the transporters can be affected by microRNA dysregulation; ABCB5 transporter is highly expressed in colon cancer cell lines with downregulated miR-522 expression and renders these cells resistant to doxorubicin treatment (182). miR-522 binds to the ABCB5 mRNA 3'-UTR and overexpression of miR-522 reverse chemoresistance to doxorubicin (182). Similarly, 5-fluorouracil resistance in microsatellite instable colon cancer [caused by deregulated miR-21 or miR-155 (124, 138) as mentioned in detail later] can be enhanced by downregulation of miR-23a resulting in higher expression of the direct target ABCF1 (156).

Similar examples exist across the board: in gastric cancer for example, downregulation of miR-508-5p was identified as a reason for multidrug resistance (180). miR-508-5p represses the expression of P-glycoprotein and the transcription factor zinc ribbon domain-containing 1 (ZNRD1) that is an important factor for *MDR1* gene translation (180). Loss of miR-508-5p decreased drug sensitivity in gastric cancer *in vitro* and *in vivo*, whereas ectopic expression of miR-508-5p overcomes drug resistance (180).

In pancreatic cancer cell lines, expression of the transporter ABCC1 is controlled by miR-1291 binding to the 3'-UTR (118). miR-1291 is often downregulated in pancreatic cancer resulting in an increased expression of ABCC1 that finally leads to higher efflux rate of toxic substances (257, 258). This is the reason for

resistance to many chemotherapeutics, such as anthracyclines (e.g., doxorubicin), platinum derivatives, and the folate antagonist methotrexate (257, 258). Another transporter, called ATP7A (ATPase Cu<sup>2+</sup> transporting alpha polypeptide), is upregulated in *in vitro* models of resistant pancreatic tumors due to decreased expression of miR-374b (174) and increased ATP7A protein expression is at least partially responsible for cisplatin resistance in pancreatic cancer model systems (174).

Downregulation of miR-122 in liver tumors results in high expression of ABC transporter proteins and causes increased drug export of doxorubicin in liver cancer patients (114). Similarly, ABCB1 transporter expression is upregulated in hepatocellular cancer cells when the posttranscriptional regulator miR-223 is downregulated and the result is again resistance to doxorubicin treatment (259).

Downregulation of microRNAs let-7g and let-7i results in increased expression of ABCC10 that in turn is responsible for resistance to cisplatin therapy in esophageal cancer patients (102).

An important barrier for oral anticancer drugs is represented by intestinal epithelial cells of the GI tract (256, 260). The absorption of most nutrient components as well as drugs is related to a variety of influx transporters such as members of the SLC transporter family (256). The expression pattern of the SLC transporter varied according to the differentiation status of intestinal epithelial cells which is controlled by microRNAs (261). Therefore, changes in the expression level of microRNAs have most probably an important influence on the drug uptake rate (261). Up to now the role of microRNAs for the expression level of SLC transporter have been studied only in cell culture models for colon carcinoma, liver, pancreatic, and gastric tumors (115, 183). In colon cancer cells, expression of miR-92b reduces the amount of SLC15A and SLC15A1 transporter resulting in decreased drug absorption (183). In the context of liver and pancreatic tumors miR-29a, miR-29b, and miR-124 target SLC16A1 and reduce the expression of this transporter (115). Recently, it was shown that miR-939 targets direct SLC34A2 in gastric cancer (184). In 5-fluorouracil-resistant gastric cancer, miR-939 is downregulated and results in increased expression level of SLC34A2. The transport protein SLC34A2 acts as mediator of miR-939 and activates the Ras/MEK/extracellular signal-regulated kinase (ERK) pathway which is known to be deregulated often in cancer and to cause resistance to chemotherapy (184). In *in vitro* models of gastric cancer, overexpression of miR-939 strongly decreased MEK1/2 phosphorylation as well as Raf-1 level, whereas SLC34A2 restoration rescued these effects (184).

Also for some drug-metabolizing enzymes posttranscriptional regulations by miRNAs have been proven (256, 262, 263). Due to their pivotal role in maintaining chemical and functional homeostasis of cells, cytochrome P450 enzymes are strictly controlled. Under physiological conditions, cytochrome P450 enzymes are involved in the regulation of endogenous molecules like bile acids and steroids and under pathological conditions in the case of chemotherapy these enzymes are important in regard to drug metabolism. Deregulated expression of cytochrome P450 enzymes is linked to drug resistance and therapy failure (264).

For example, miR-378 targets mRNA coding for CYP2E1 and reduces the expression level of CYP2E1 protein in cell culture

models of liver tumors (175, 265). In liver cancer patients, CYP2E1 expression is increased while miR-378 is downregulated (175, 265). Also, a direct regulation of CYP1B1 by miR-27b was demonstrated in hepatocellular cancer cell lines (164). Decreased expression of miR-27b results in high expression level of CYP1B1 and renders by this liver tumor resistant to docetaxel treatment (164).

In pancreatic cancer cells, overexpression of miR-27b leads to downregulation of CYP3A4 protein and results in drug resistance to cyclophosphamide because CYP3A4 is necessary for drug activation (165). MicroRNA-based regulation of enzymes involved in phase II reactions are less analyzed but nevertheless, in the context of esophageal cancer, regulation of glutathione S-transferase P1 (GSTP1) was found to be regulated by miR-133a (121). Reduced expression of the tumor suppressor miR-133a resulted in increased level of GSTP1 protein (121). In phase II detoxification reactions—including inactivation of platinum derivatives and alkylating reagents—GSTP1 catalyses the addition of glutathione to the drug activated during phase I reactions with electrophiles (249, 250).

A more specific influence of non-coding RNAs on drug metabolism was demonstrated for 5-fluorouracil in liver and colon tumors (163, 178). Dihydropyrimidine dehydrogenase, an important enzyme in 5-fluorouracil metabolism, is repressed by miR-494 in colon tumors and by miR-27a as well as miR-27b in liver cancer (163, 178). The fact that the translation of one and the same enzyme in two different tissues is under the control of different miRNAs underlines the tissue-specific regulation and fine-tuning of protein expression that is exerted by miRNAs.

In liver cancer, the translation of two of the most important targets of chemotherapeutic agents, dihydrofolate reductase and thymidylate synthase, are repressed by upregulation of miR-215 (148). Reduced expression of dihydrofolate reductase and thymidylate synthase leads to the development of insensitivity to doxorubicin treatment (148).

Thymidylate synthase is the target of 5-fluorouracil therapy and this enzyme is downregulated by increased expression of miR-192 and miR-215 in colon cancer patients (129). In this case, altered microRNA expression results in down-modulation of the drug target and leads to therapy failure. In addition, miR-192 and miR-215 alter the cell-cycle control at multiple levels and prevent progression into the S-phase leading to 5-fluorouracil resistance (129).

A similar case was observed in pancreatic tumors where ribonucleotide reductase regulatory subunit M2 (RRM2) the target of gemcitabine is under direct control of miR-211 and let-7a (101, 147). Decreased expression of miR-211 and let-7a results in higher RRM2 protein level and renders the tumors resistant to gemcitabine (101, 147).

## Deregulation of Cell-Cycle, DNA Repair Pathways and Alteration in Death Pathways

Impaired cell cycle regulation and alteration of cell death pathways are common causes of drug resistance (243, 266). Increased cell cycle progression and reduced cell death rate lead to accumulation

of mutations and uncontrolled cell proliferation, a hallmark of tumor cells (267). Errors in the DNA-damage response program pathways [nuclear excision repair (NER), base excision repair (BER), and DNA mismatch repair (MMR)] play an important role in cancer progression and chemoresistance (268–271). A complex interaction interplay exists between non-coding RNAs and the DNA-damage pathways: on one hand the DNA-damage pathway induces the expression of several non-coding RNAs especially of microRNAs and on the other hand non-coding RNAs regulate directly the expression of several genes involved in DNA-damage pathway. This interaction is cell type specific and dependent on the intensity and nature of DNA damage (272–276).

LncRNA HOX transcript antisense RNA (HOTAIR) is highly expressed in a broad variety of solid tumors including liver, colorectal, pancreatic, and GI stromal tumors (39, 40, 277). LncRNA HOTAIR reprograms chromatin organization together with the polycomb repressive complex PRC2 (40). Upregulation of lncRNA HOTAIR results in higher expression level of members of the PRC2 complex (SUZ12, EZH2, and H3K27me3) (40). Therefore, increased lncRNA HOTAIR expression is associated with a genome-wide reprogramming *via* PRC2 mediated epigenetic silencing of chromatin (40). In addition, lncRNA HOTAIR downregulates cyclin-dependent kinase inhibitor 1 [p21(WAF/CIP1)] (41) causing the loss of an important regulator of the G<sub>1</sub> and S phase progression (38, 278, 279). Due to the fact that p21(WAF/CIP1) represents a major target of p53 activity DNA damage in lncRNA HOTAIR expressing tumor cells don't go into cell cycle arrest and this promote cisplatin resistance (38, 41, 278, 279).

In esophageal, gastric, colorectal, and hepatocellular cancer as well as cholangiocarcinomas, lncRNA taurine-upregulated gene 1 (TUG1) is involved in causing resistance to chemotherapy (79–85). In tumor tissue, lncRNA TUG1 is upregulated and promotes cell growth by increased transcription of the *Bcl-2* gene and epigenetic silencing of cyclin-dependent protein kinase inhibitors (p15, p16, p21, p27, and p57) and proapoptotic genes (caspase-3, caspase-9, and Bax) (79–85). Therefore, lncRNA TUG1 is an excellent example for the fact that non-coding RNAs target simultaneously the expression of different genes; beside increasing the expression level of the antiapoptotic protein *Bcl-2*, expression of key players in the caspase-mediated apoptosis pathway are inhibited together with different cyclin-dependent protein kinase inhibitors. This results in decreasing the G<sub>0</sub>/G<sub>1</sub> arrest during cell cycle and reduces the apoptosis rate of the tumor cells. Most probably lncRNA TUG1 has also a role in the EMT (83, 85) that increases resistance to drug treatments further as outlined in detail below.

Also, the lncRNA promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR) is often deregulated in different GI tumors like gastric, colorectal, and hepatocellular cancer as well as cholangiocarcinoma (71–74). In all these tumors, upregulation of lncRNA PANDAR results in increased proliferation rate and reduced apoptosis (71–74). LncRNA PANDAR interacts with the transcription factor NF- $\kappa$ B, an important regulator for transcription of proapoptotic genes (70). This interaction between lncRNA PANDAR and NF- $\kappa$ B results in decreased expression of proapoptotic genes and eventually leads to drug resistance (71–74).

lncRNA urothelial carcinoma associated 1 (UCA1) mediates resistance to doxorubicin treatment in gastric cancer (94). In *in vitro* systems, knockdown of lncRNA UCA1 overcomes the doxorubicin resistance due to an increased expression of PARP and reduced expression of Bcl-2 resulting in higher apoptosis rate (94).

Furthermore, it was shown that lncRNA UCA1 sequesters miR-204-5p in colorectal cancer and reduces the level of this microRNA in cancer cells (90). The consequence is enhanced cell proliferation and 5-fluorouracil resistance (90).

Another example of non-coding RNAs influencing cell-cycle is lncRNA adriamycin resistance associated (ARA) (31, 32). lncRNA ARA was found to be overexpressed in doxorubicin-resistant liver cancer cell lines compared to the parental cell lines (31). Downregulation of lncRNA ARA results in cell-cycle arrest in G2/M phase, suppressed proliferation, increased apoptotic cell death and, as expected, a reduced resistance against doxorubicin (31, 32). Furthermore, lncRNA ARA is involved in the regulation of multiple signaling pathways including the MAPK-pathway (31, 32). Beside lncRNA ARA the lncRNA upregulated in hepatocellular carcinoma (URHC) is found among the most upregulated lncRNAs in hepatocellular carcinoma. One target of lncRNA URHC is the tumor-suppressor ZAK (97). Downregulation of ZAK *via* lncRNA URHC results in increased cell proliferation and inhibits apoptosis (97).

In pancreatic cancer, lncRNA HOXA transcript at the distal tip (HOTTIP) upregulates the homeobox-transcription factor HOX13 resulting in deregulation of the cell cycle as well as gemcitabine resistance (49, 50).

Downregulation of lncRNA LOC285194 in esophageal cancer results in resistance to chemoradiotherapy (radiation in combination with platinum- or paclitaxel-based chemotherapy) by influencing cell-cycle progression and non-apoptotic cell death pathway *via* regulating VEGF receptor 1 (60).

In contrast, lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) is strongly overexpressed in esophageal tumor tissue and binds miR-107 and miR-217 (62, 63). miR-107 and miR-217 decoy translates in reduced activity of the ATM-CHK2 signaling pathway leading to reduced cell-cycle arrest and cell death as response to DNA damage (61, 63) and overexpression of the transcription factor B-Myb—an important regulator for G1/S and G2/M cell-cycle progression and cell survival (62, 63).

In addition, several microRNAs have been identified as regulators for cell cycle progression and induction of cell death pathways. Therefore, deregulated microRNA expression pattern is often a reason for drug resistance in GI tumors.

Colorectal cancers with upregulated miR-203 are resistant to oxaliplatin (136). Failure of oxaliplatin therapy is caused by miR-203 mediated downregulation of the important mediator protein for DNA damage response ATM (136). As reaction to DNA damage, ATM induces the expression of DNA repair proteins, interrupts the cell cycle, and induces cell death in the case of extended DNA damage (280). Oxaliplatin resistance can also be caused by upregulation of miR-503-5p in colorectal cancer (179). Increased expression of miR-503-5p results in downregulation of the apoptotic protein p53 upregulated modulator of apoptosis

(PUMA) and leads to resistance to oxaliplatin-induced apoptosis (179). In colon cancer tissues, downregulation of miR-320 is linked to resistance to 5-fluorouracil therapy (169). Among the targets for miR-320 is the transcription factor SOX4 which is involved in inhibition of p53-mediated apoptosis as well as the cell cycle regulators FOXM1 and FOXQ1 both known to have oncogenic potential (169, 170).

In colorectal cancer cells, miR-21 overexpression results in inhibition of the MMR proteins MSH2 and MSH6, two important proteins for DNA damage recognition and repair (138). Inhibition of MSH2 and MSH6 leads to reduced G2/M cell-cycle arrest caused by 5-fluorouracil induced DNA damage and lower apoptosis rate *in vitro* and *in vivo* (138). Therefore, miR-21 overexpression reduces the therapeutic efficacy of 5-fluorouracil-based chemotherapy in colorectal cancer treatment (138). Furthermore, it was proven that the core mismatch repair proteins MSH2, MSH6, and MLH1 are also downregulated by miR-155 potentially contributing to drug resistance (124). According to another study, 5-fluorouracil resistance in colorectal cancer cells can also be mediated by increased expression of miR-31 causing cell cycle deregulation and reduced apoptosis rate (167, 168). Efficacy of 5-fluorouracil treatment in colorectal cancer patients can also be limited due to upregulation of antiapoptotic proteins like X-linked inhibitor of apoptosis (XIAP) and ubiquitin-conjugating enzyme E2N (UBE2N) as a consequence of decreased miR-96 expression (185) or due to upregulation of the antiapoptotic proteins Bcl-2, Bcl-2-like protein 11 (BIM), or Bcl-2-like protein 2 (Bcl2L2) by reduced expression of miR-129, miR-10b, or miR-195, respectively (106, 117, 131). In other colon cancer studies, reduced expression levels of miR-365, miR-1915, and miR-34a have been described as reason for increased expression of BCL-2 (128, 172, 173).

Increased Bcl-2 expression has been identified as a reason for resistance to 5-fluorouracil in other GI tumors, too, but the posttranscriptional regulation of mRNA coding for Bcl-2 is under the control of different miRNAs; e.g., in gastric cancer diminished expression of miR-204 is the reason (281). According to another study upregulation of Bcl-2 is caused by lower miR-15b and miR-16 expression level and leads to drug resistance in gastric cancer cells due to reduced apoptosis (125). miR-25 overexpression was related to cisplatin resistance in gastric cancer cells (160). miR-25 targets directly mRNAs coding for tumor suppressors like FOXO3a, ERBB2, and F-box/WD repeat-containing protein 7 (FBXW7) (157–160). All these proteins are involved in cell cycle regulation and apoptosis (160, 282, 283). Upregulation of miR-223 targets FBXW7 and leads to cell-cycle deregulation and cisplatin resistance in gastric tumors (154). Furthermore, upregulation of miR-103/107 results in decreased expression of caveolin-1 in gastric cancer cells (109). The tumor suppressor caveolin-1 is a counter regulator for the Ras-p42/p44 MAP kinase pathway and due to the downregulation by miR-103/107 increased activity of the Ras-p42/44 Map kinase pathway results in increased cell cycle progression and reduced cell death (107, 108). In gastric cancer, increased cell cycle progression is also caused by increased expression of miR-215 resulting in reduced expression of the tumor suppressor retinoblastoma 1, an important cell cycle regulator (149, 150). Upregulation of miR-106a targets FAS and inhibits the extrinsic apoptotic pathway in gastric cancer (110, 111).

In turn, reduced amount of FAS leads to increased cell proliferation, reduced apoptosis rate, and drug resistance (110, 111).

Overexpression of miR-21 inhibits cell cycle arrest resulting in increased cell proliferation, reduced apoptotic rate, gemcitabine, and 5-fluorouracil resistance in pancreatic cancer (284–286). Similarly, in other pancreatic cancer studies, miR-21 overexpression results in reduced level of PTEN and Bcl-2 leading to activation of AKT-mTOR pathway, reduced apoptosis, and resistance against gemcitabine treatment (140, 141). Increased expression of miR-214 represses directly ING4 in pancreatic tumor (287). This impairs cell-cycle arrest, DNA repair as well as apoptosis and results in resistance to gemcitabine treatment (287). The expression of the important proapoptotic protein BIM is reduced by miR-17-5p in pancreatic cancer and results in decreased apoptotic rate leading to resistance to gemcitabine treatment (127). Therapy failure is also caused by the repression of a tumor suppressor network involved in cell cycle and apoptosis regulation composed of PDCD4, BTG2 and NEDD4L by the combined action of miR-21, miR-23a, and miR-27a (145, 146). Furthermore, overexpression of miR-1246 results in decreased expression of cyclin-G2 and impairs the cell cycle regulation resulting in resistance to gemcitabine (116). Recently, miR-1307 was identified to be responsible for FOLFIRINOX resistance in pancreatic cancer (120). miR-1307 is upregulated in *in vitro* models of FOLFIRINOX-resistant pancreatic cancer as well as in patient derived material compared to the surrounding tissue (120). Reduced apoptosis rate and an extended acceptance of DNA damage seem to be the consequence of higher miR-1307 expression (120).

In hepatocellular carcinoma, the liver specific miR-122 is downregulated and as consequence the expression of the target gene *CCNG1* is increased (113). High level of cyclin G1 protein is found in several human tumors and results in reduced cell cycle control in the G2/M phase and modulation of p53 activity (113, 114). This results in reduced DNA-repair and diminished apoptotic rate (113, 114). As already mentioned above, ABC transporter proteins are highly expressed in liver tumors due to the missing posttranscriptional regulator miR-122 (114). All these effects caused by miR-122 downregulation promote doxorubicin resistance in liver cancer patients (113, 114). Another reason for doxorubicin resistance in liver cancer is based on reduced expression of miR-26b (161). Among the miR-26b targets in liver are the NF- $\kappa$ B activating proteins TAB3 and TAK1 (161, 162). Therefore, a reduced expression of miR-26b results in increased activation of NF- $\kappa$ B and promotes drug resistance (161, 162). Also, downregulation of miR-101 is described as reason for resistance to doxorubicin in hepatocellular carcinoma (105). The antiapoptotic protein Mcl-1 is among the targets of miR-101 and high levels of Mcl-1 renders liver tumor cells resistant to doxorubicin treatment (105). Furthermore, doxorubicin treatment failure in liver cancer patients has been connected to downregulation of miR-199a-3p (133). Besides targeting mTOR and c-Met, miR-199a-3p influences cell cycle regulation (133). Decreased miR-199a-3p level results in downregulation of the G1-checkpoint CDK inhibitors p21 (CDKN1A) and p27 (CDKN1B) and abrogate the G1 arrest following damage to DNA (132, 133). In another study, downregulation of the G1 inhibitor CDKN1A in hepatocellular carcinoma was linked to upregulation of miR-519d (181). Consequently the

apoptotic rate is reduced due to downregulated miR-199a-3p as well as upregulated miR-519d expression (133, 181).

Another important tumor suppressor protein involved in resistance to anticancer drugs is PTEN because it is a main regulator for PI3K-AKT-mTOR pathway which is often hyperactivated in cancer and is one of the drivers for tumor growth and survival (288, 289). PTEN itself is regulated by different microRNAs in different GI tumors, e.g., by miR-21 in liver and gastric cancer, miR-22 in p53-mutated colon cancer and miR-17-5p in colorectal cancer (126, 142–144, 151). In all cases, upregulation of microRNAs results in decreased PTEN level in the tumor cell and subsequent activation of AKT-mTOR pathways resulting in resistance to cisplatin (gastric cancer), paclitaxel (p53-mutated colon tumor), and FOLFOX (colorectal cancer) (126, 142–144, 151). Downregulation of PTEN due to overexpression of miR-19a and miR-19b in gastric cancer results in multi-drug resistance (134).

Furthermore, mTOR is an important regulator under physiological as well as pathological conditions. In p53 mutant colorectal cancer, mTOR is downregulated by miR-338-3p and results in resistance to 5-fluorouracil treatment (171). Indeed, inhibition of miR-338-3p in cell culture models restored sensitivity to 5-fluorouracil (171) likely due to increased autophagy and reduced apoptosis following decrease in mTOR expression (171, 290).

Autophagy is a further mechanism for chemoresistance (51, 291–293). In liver cancer, upregulation of lncRNA HULC activates autophagy by increasing the expression of ubiquitin-specific peptidase 22 (USP22) which in turn prevents the ubiquitin-mediated degradation of silent information regulator 1 (SIRT1) by removing the conjugated polyubiquitin chains from SIRT1 (51). Autophagy causes resistance to oxaliplatin, 5-fluorouracil and epirubicin treatments in liver tumors (51). In addition, lncRNA HULC downregulates the expression of microRNAs that target directly the 3'-UTR of USP22 (miR-6825-5p, miR-6845-5p, and miR-6886-3p) in liver cancer cells and prevents by this inhibition of USP22 at translational level (51).

lncRNA MALAT-1 is highly expressed in gastric cancer cells resistant to 5-fluorouracil and cis-platin, respectively, compared to parental gastric cancer cells (67). lncRNA MALAT-1 quenches miR-23b-3p and subsequently increases the expression of ATG12, an important regulator of autophagy (67).

In oxaliplatin-resistant colon cancer, miR-409-3p is downregulated so that the direct target Beclin-1 is expressed and induces autophagy (176). Overexpression of miR-409-3p results in low autophagic activity and overcomes oxaliplatin resistance in model systems of colon cancer (176).

## Induction of EMT

Drug resistance can be caused by EMT (294, 295). Several EMT-related signaling pathways are well known to be involved in mediating drug resistance in tumors (22, 295–297). Cells undergoing EMT have several features in common with cancer stem cells (e.g., increased drug efflux pumps and antiapoptotic effects) and furthermore EMT is instrumental for generation and maintenance of cancer stem cells (22, 295, 297).

The lncRNA plasmacytoma variant translocation 1 (PVT1) has been found to be elevated in nearly all GI tumors including gastric,

esophageal, pancreatic, colon, and liver cancers (75–77, 298). Increased expression of lncRNA PVT1 results in EMT and drug resistance (75–77).

The tumor suppressor lncRNA LEIGC prevents normal cells to undergo EMT. Therefore, the reduced expression of lncRNA LEIGC in gastric cancer fosters EMT and results in resistance to 5-fluorouracil treatment (54, 55).

Upregulation of lncRNA HULC has been correlated to induce EMT and suppressed apoptosis in gastric tumors, leading to cisplatin resistance (52, 53).

Increased expression of lncRNA-activated by TGF- $\beta$  (lncRNA-ATB) in liver cancer results in competition with members of the miR-200 family for binding sites in the 3'-UTR of mRNAs coding for the transcription factors ZEB1 and ZEB2 (33). In turn, high expression of ZEB1 and ZEB2 causes EMT and increased drug resistance (33).

In pancreatic cancer, the lncRNA MALAT-1 is a regulator of EMT (64, 65). In addition, the lncRNA MALAT-1 suppress G2/M cell cycle arrest and apoptosis leading to resistance to gemcitabine treatment (65). As demonstrated by this example, the same lncRNA can induce resistance to chemotherapy by regulating different mechanisms at the same time.

Induction of EMT and resistance to gemcitabine treatment in pancreatic cancer cells can also be caused by miR-223 overexpression (153). Inhibition of miR-223 restored the sensitivity of pancreatic cancer cell lines to gemcitabine treatment (153). Similarly, gemcitabine resistance in pancreatic cancer can also be caused by downregulation of microRNAs as demonstrated for miR-200 (miR-200a, miR-200b, and miR-200c) and let-7 family resulting in EMT (100, 135).

In colon cancer cells, downregulation of miR-147 results in EMT and increases the phosphorylation rate of AKT (123). Beside the activation of the PI3K-AKT pathway, the lower expression level of miR-147 also activates the TGF- $\beta$  pathway and eventually leads to resistance to gefitinib treatment (123). Increased expression of miR-224 in colon cancer tissue was identified as another reason for resistance to 5-fluorouracil treatment. Increased miR-224 expression translates in increasing phosphorylation rate of ERK and AKT, resulting in activation of both pathways (155). In addition, miR-224 seems to activate also EGFR dependent- and NF- $\kappa$ B-signaling pathway leading to EMT (155).

## Cancer Cell Stemness

A further reason for drug resistance is the presence of cancer stem cells. Cancer stem cells are well known for being refractory to chemotherapies and therefore cause therapy failure and tumor recurrence or progression (299–305). Once again non-coding RNAs especially lncRNAs and microRNAs are involved in sustaining the cancer stem cell niche (95, 306–309).

The lncRNA urothelial carcinoma associated 1 [identical with lncRNA CUDR (cancer upregulated drug resistant)] is strongly expressed in different tumors; among these, gastric, hepatocellular, pancreatic, colorectal cancers, and esophageal squamous cell carcinoma (94–96, 310–314). lncRNA UCA1 binds to several microRNAs in different tumors (e.g., miR-216b in liver cancer, miR-204 in esophageal and colon cancer, miR-27b in gastric cancer) and influences entire transcriptional programs as well as

response toward therapy (90, 92, 312, 314, 315). Well-established upregulated targets of lncRNA UCA1 are members of the Wnt- $\beta$ -catenin signaling pathway, several transcription factors and cell division regulators (87, 93). For stem cells, the Wnt- $\beta$ -catenin pathway is of pivotal importance for cell self-renewal and mediating drug resistance (316, 317). Overexpression of lncRNA UCA1 results in resistance to cancer treatments with tamoxifen, 5-fluorouracil, gemcitabine, cisplatin, doxorubicin, imatinib, and tyrosine-kinase inhibitors targeting EGFR (90, 94, 96, 314).

Silencing of lncRNA UCA1 in *in vitro* and *in vivo* systems proved the oncogenic role of lncRNA UCA1 in gastric cancer (94, 96). Reduced expression level of lncRNA UCA1 results in reduced proliferation rate, increased apoptosis rate and overcomes the resistance to doxorubicin (94, 96). Furthermore, lncRNA UCA1 is a direct regulator of the PI3K-AKT-mTOR pathway (96) which is often found to be deregulated in human cancers and is known to contribute to chemoresistance of cancer cells (318, 319). In another study, overexpression of lncRNA UCA1 was shown to cause reduced miR-27 expression causing diminished apoptosis of gastric cancer cells due to increased Bcl-2 protein level in combination with reduced cleaved caspase-3 (92). This results in multidrug resistance of gastric tumors (92).

Overexpression of lncRNA UCA1 is also a reason for chemoresistance against 5-fluorouracil treatment in colon cancer (90). lncRNA UCA1 causes resistance by binding miR-204-5p and consequently upregulating the expression of its target genes Bcl-2, RAB22A, and CREB1 (90). miR-21 was identified as an important player in regard to failure of 5-fluorouracil therapy in colon cancer patients (139). miR-21 is able to increase the number of undifferentiated cancer stem cells during 5-fluorouracil treatment and contributes by this to therapy failure (139).

In liver cancer, lncRNA UCA1 contributes to chemotherapy resistance and malignant transformation of hepatocyte-stem cells (88, 93, 95, 320–322). lncRNA UCA1 increases directly the transcription rate of the oncogene c-myc well known to be involved in drug resistance as well as in activating stem-cell like properties in hepatocarcinoma (86, 89, 323–325). Furthermore, lncRNA UCA1 also induces the expression of lncRNA HULC (highly upregulated in liver cancer) in liver cancer and lncRNA HULC in turn stimulates the activity of the Wnt- $\beta$ -catenin pathway (88). In addition, lncRNA UCA1 forms a complex with the cell-cycle regulator cyclin-D which enhances the expression of lncRNA H19 by inhibiting the methylation of the lncRNA H19 promoter (89, 95). High level of lncRNA H19 induces the telomerase activity and enhances the length of telomere thereby supporting the stem cell properties (35, 89, 326). Another effect of lncRNA UCA1 is the enhanced phosphorylation of the tumor suppressor retinoblastoma protein 1 (RB1). RB1 phosphorylation results in increased cell cycle progression and in interaction of the phosphorylated retinoblastoma protein 1 with the SET1A complex. Such interaction catalyses the transcription-activating methylation of histone H3 lysine-4 on several gene promoters including telomeric repeat-binding factor 2 promoter an important component for the telomerase extension process (91, 320).

In liver cancer as well as in pancreatic, gastric, esophageal, and colon cancers a critical role in inducing the transformation of stem cells into cancer stem cell has been demonstrated

for lncRNA HOTAIR (45, 95, 327–331). LncRNA HOTAIR is a strong activator for expression of *OCT4*, *RNF51*, *CD44*, and *CD133* genes—all these proteins are involved in reprogramming the gene network to acquire cancer stem cell properties (46, 47). LncRNA HOTAIR expression causes resistance against cisplatin and doxorubicin treatment in liver cancer model systems (332) and renders gastric tumors resistant to cisplatin therapy by binding miR-126 and activating the PI3K-AKT-mTOR pathway (48). In the context of several GI cancer stem cells, it has been shown that lncRNA HOTAIR downregulates the expression of histone methyltransferase SETD2 and reduces the phosphorylation rate of SETD2 resulting in reduced trimethylation of histone H3 lysine-36 on several gene promoter, e.g., Wnt inhibitory factor-1 (WIF-1) (44, 45, 331, 333). Reduced WIF-1 expression leads to activation and increased signaling through the Wnt- $\beta$ -catenin pathway (44, 45). Furthermore, the modulated chromatin organization account for a reduced efficiency of the mismatch repair system and damaged DNA can escape from corrections leading to microsatellite instability (MSI) and altered expression of cell cycle regulators as well as reduced apoptosis (124, 327, 331, 334, 335). In addition, lncRNA HOTAIR induces accumulation of replication errors by hindering the complex formation of MSH2 with MSH6; one essential dimer for DNA mismatch recognition and repair (42, 43, 124, 138, 336).

In pancreatic cancer, the oncogenic lncRNA MALAT-1 contributes to the expression of the cancer stem cell marker CD133, CD44, CD24, and aldehyde-dehydrogenase (65, 66, 337). In addition, the expression of the core pluripotent factors OCT4, NANOG, and SOX2 are also under the control of lncRNA MALAT-1 (66). LncRNA long intergenic ncRNA regulator of reprogramming (linc-ROR) inhibits the expression of p53 and activates by this the transcription factor ZEB1 in pancreatic cancer (56). ZEB1 in turn suppress the expression of the miR-200 family that leads to maintenance of pancreatic cancer stemness and induces EMT known to be responsible for paclitaxel resistance in pancreatic cancer patients (56, 57). Downregulation of miR-205 results in increased expression of stem cell markers OKT3, OKT8, and CD44 in pancreatic cancer tissue and is linked to gemcitabine resistance (137). Re-expression of miR-205 is able to overcome the gemcitabine resistance in pancreatic cancer model systems (137).

The lncRNA-34a mediates an increase in self-renewal of colon cancer stem cells and induce Wnt as well as NOTCH signaling pathways *via* sequester miR-34a expression (98, 99).

In hepatocellular carcinoma, the lncRNA is involved in regulating core pluripotent factors (OCT-4, NANOG, SOX2) necessary for the stem cell like phenotype and causes resistance to chemotherapy (59). LncRNA linc-ROR competes with miR-145 for the same binding sites present in the mRNAs coding for OCT-4, NANOG, and SOX2 (58). Presence of lncRNA linc-ROR prevents the binding of miR-145 to the mRNA of the core pluripotent factors resulting in translation of these mRNAs and maintains the stem cell phenotype (58). Furthermore, the expression of CD133, another cancer stem cell marker, is directly induced by lncRNA linc-ROR (59).

miR-130b is connected to cancer stem cells growth in liver tumors (119). Increased expression of miR-130b targets directly

the mRNA coding for tumor protein 53-induced nuclear protein 1 and reduces the expression level of the corresponding protein (119). Furthermore, high level of miR-130b renders liver tumor cells resistant to doxorubicin treatment (119). Another reason for doxorubicin resistance in liver cancer patients is downregulation of the tumor suppressor miR-101 resulting in increased protein expression of enhancer of zeste homolog 2 (EZH2) (103, 104). EZH2 is a histone-lysine N-methyltransferase enzyme that silence Wnt-pathway antagonists and other tumor suppressor genes on the transcriptional level by histone methylation (338). Overexpression of EZH2 is positively correlated with increased Wnt- $\beta$ -catenin signaling (338).

miR-221 is over-expressed in 5-fluorouracil-resistant esophageal tumors (152). The mechanisms of resistance is mediated *via* downregulation of the direct target dickkopf-related protein 2 (DDK2) and subsequent activation of the Wnt- $\beta$ -catenin pathway (152). Furthermore, increased miR-221 expression fosters EMT and facilitates the formation of tumor stem cells (152).

In colon cancer stem cells, miR-451 was found to be down-regulated compared to colon cancer cells (177). Reduced level of miR-451 seems to be essential for the self-renewal of colon cancer stem cells (177). In addition, expression of ABCB1 transporter is increased in colon cancer stem cells due to lack of miR-451 posttranscriptional downregulation resulting in resistance to irinotecan treatment (177).

miR-1182 is often downregulated in gastric cancer tissue (112). One direct target of miR-1182 is telomerase reverse transcriptase (hTERT), an enzyme that is involved in controlling the length of telomere. Overexpression of hTERT due to missing transcriptional regulation by miR-1182, results in cell immortality and stem-cell property of gastric cancer cells (112).

## Targeted Therapies and Drug Resistance

For GI cancer several targeted therapies exist (Table 3) (339–345). They are used alone or in combination with chemotherapy. Unfortunately in most cases the patients develop resistance also against these targeted therapies and the above outlined general principles of drug resistance based on non-coding

**TABLE 3** | Approved targeted therapies for GI cancer.

GI cancer	Drug	Target
Gastric cancer	Trastuzumab	HER2
	Ramucirumab	VEGFR-2
	Pembrolizumab	PD-1
Hepatocellular cancer	Sorafenib	RAF, VEGFR-2, VEGFR-3, PDGFR, c-KIT
Colon cancer	Cetuximab,	EGFR
	panitumumab	
	Bevacizumab	VEGF
	Regorafenib	VEGFR-1, VEGFR-2, VEGFR-3, BRAF, c-KIT, RET, PDGFR
Colon cancer with MSI-H	Pembrolizumab	PD-1

HER2, human epidermal growth factor receptor 2; VEGFR, vascular endothelial growth factor receptor; PD-1, programmed cell death protein-1; RAF, rapidly accelerated fibrosarcoma; PDGFR, platelet-derived growth factor receptor; c-KIT, SCFR, mast/stem cell growth factor receptor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; RET, rearranged during transfection; MSI-H, microsatellite instability-high.

RNA dysregulation are involved. Beside that non-coding RNAs interfering with the targeted protein itself or (up-)regulating the targeted signal pathway are involved in drug resistance (342). Furthermore, therapy failure can be related to activation of alternative signal pathways by non-coding RNAs (68, 342).

Recently, it was demonstrated that resistance to cetuximab in colon cancer patients and in *in vitro* 3-D-cell culture models can be caused by overexpression of lncRNA MIR100HG (68). Two microRNAs, miR-100, and miR-125b, are generated from lncRNA MIR100HG and these microRNAs downregulate in a concerted way five negative regulators of the Wnt/ $\beta$ -catenin pathway resulting in increased Wnt signaling (68). This kind of cetuximab resistance can be overcome by inhibition of Wnt signaling, underscoring the potential clinical relevance of the interactions between EGFR and Wnt/ $\beta$ -catenin pathways (68). Increased miR-125b expression is also correlated with trastuzumab resistance in HER2-positive gastric cancer patients but up to now the molecular basis for this resistance is unclear (346). Sorafenib resistance in hepatocellular carcinoma is caused by lncRNA TUC338 (78). RAS protein activator like-1 (RASAL-1) is a direct target of lncRNA TUC338 and high expression of lncRNA TUC338 inhibits the RASAL-1 expression resulting in activation of RAS-signaling (78). According to another *in vitro* study, reduced expression of miR-193b leads to higher expression of the antiapoptotic protein Mcl-1 and renders hepatocellular carcinoma cells resistant to sorafenib treatment (130).

## Non-Coding RNAs as Potential Biomarkers of Resistance and Novel Therapeutics: Promises and Hurdles

Our review summarizes most of the current evidence supporting the role of non-coding RNAs in resistance to chemotherapy and targeted agents. It is likely that, in the near future, given the promising and exciting results obtained with the use of immunotherapy in gastroesophageal (347) and colorectal cancer (348, 349), new data will emerge on the already known regulation of PD-1, PD-L1, and CTLA-4 by non-coding RNAs and response to nivolumab and pembrolizumab (350–352).

The contribution of non-coding RNAs in resistance mechanisms to a broad range of anticancer treatments makes their use as biomarkers or novel therapeutics quite promising but several challenges remain.

Given microRNAs and, to a lesser extent, other non-coding RNAs can be reliably detected in tissues and biofluids such as plasma, serum, and urine, it is tempting to hypothesize the use of non-coding RNA based tools to predict and monitor resistance to anticancer treatments. Few studies have already tested the validity of microRNAs as biomarkers of response to anticancer treatment in other cancers such as prostate (353), chronic lymphocytic leukemia (354), and sarcomas (355). In colorectal cancer, we (356) and others (357–359) have tested the contribution of a single nucleotide polymorphism (SNP) in the binding site of let-7 in the *KRAS* 3'UTR in predicting benefit from anti-EGFR treatment with conflicting results across different trials. Despite the good reproducibility of the assay, the predictive value of the test was not confirmed in all trials likely due to use of cetuximab in different

context (neoadjuvant, adjuvant and metastatic colorectal cancer, respectively). Similarly the analysis of a SNP in miR-608 led to contradicting results in patients treated with neoadjuvant or adjuvant chemo- and radiochemotherapy in colon and rectal cancers highlighting some of the challenges in validating data obtained in retrospective series (360–363). Tissue (cancer *versus* stroma) and organ (colon *versus* rectum) specificity in non-coding RNA expression might represent potential explanations for different findings obtained in some of these studies. Beside SNPs, expression of microRNAs can be detected in fresh frozen or formalin fixed paraffin embedded tissues and serve as potential biomarker of sensitivity or resistance to treatment. Robust data have emerged from the retrospective analysis of a prospective phase III clinical trial (364). In this study, *KRAS* wild-type patients were classified based on high or low miR-31-3p expression: patients with high expression were resistant to cetuximab while patient with low expression had good and durable responses which translated in survival benefit. The miR-31 expression cutoff for the classification into high or low expression was predefined in the above study. However, one of the key challenges in validating these interesting findings will be design of a clinically approved assay that can accurately assign patients into one of these two categories. In this prospective, the use of different sources of material (i.e., primary colorectal cancer *versus* metastasis) might result in different basal expression of the microRNA and as such different scoring. Source of material and choice of reference controls represent important obstacles that might bias the definition of a threshold for high or low expression of microRNAs in tissues and biofluids. MicroRNAs can be detected in plasma, serum and urine samples and have been used for early detection and prognostic purposes in GI cancer (365–367). The use of digital droplet approaches allows the quantitative detection of copies of the microRNA of interest based on the starting volume of biofluids and, potentially overcomes or at least mitigates, the issues related to the normalization of data against reference controls, making the definition of cutoff easier to standardize. One study has reported the potential role of miR-126 in predicting and tracking response to chemotherapy and anti-VEGF treatment in colorectal cancer (368) and, with the advent of digital quantitative technologies, more studies are expected.

In consideration of their role in cancer initiation, progression and resistance to treatment, non-coding RNAs and among them microRNAs have been proposed as potential therapeutics (369). A large body of pre-clinical evidence is available on the use of anti-microRNAs or molecules re-expressing microRNAs alone or in combination with other agents in order to increase efficacy and prevent or revert drug resistance (370). Inhibition of microRNAs has been tested in clinical trials in the context of HCV infection (371, 372) and in mesothelioma (373). These trials highlighted a huge potential for microRNA-based therapeutics but at the same time pinpointed some of the criticalities in further clinical development of such approaches. miR-122 inhibition led to durable viral load reduction in both HCV trials and was associated with manageable side effects. Similarly, in mesothelioma patients treated with miR-16-loaded minicells the disease control rate was satisfactory and the toxicity profile acceptable warranting further investigations. Overall in both

approaches the risk of off-target effects represent the main hurdle to be taken into account: indeed miR-122 inhibition has been associated with risk of developing liver cancer in preclinical models (374) and, similarly, overexpression of miR-16 might lead to uncontrolled cardiac effects as proven in the phase I trial (373). These effects might be increased in combination studies in which anti-microRNAs or microRNA-conjugates are delivered together with chemotherapy leading to cumulative side effects. Therefore, a robust understanding of the biology underpinning microRNA deregulation in physiology and pathological conditions in order to implement effort that can minimize the risk of serious adverse events hampering the clinical development of microRNA-based strategies.

## CONCLUSION

Non-coding RNAs especially lncRNAs and microRNAs are important mediators for drug resistance. They function in an organ and tissue specific manner and through different molecular mechanisms. One non-coding RNA always have several targets and in the end deregulation of one non-coding RNA alters the expression level of several proteins in a tissue specific way. For example, in the case of miR-374b more than 700 genes have been identified as direct target in pancreatic tissue (174). Drug resistance is a dynamic process caused by several cell and non-cell

autonomous mechanisms. Given non-coding RNAs can simultaneously control several cancer-associated pathways, non-coding RNA dysregulation plays a crucial role in treatment resistance. Future studies will continue to shed insights in the fine interplay among lncRNA, microRNA and their target genes and might provide opportunities for more effective strategies to prevent or overcome resistance. In the interim, given non-coding RNAs and especially microRNAs can be tested in tissues and biofluids in a rapid, cost/effective and robust way. More investigational studies should explore their utility to monitor and forecast treatment response and resistance in order to personalize treatments and improve patient's outcomes.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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