

Review Article

The emerging role of long non-coding RNAs in the drug resistance of colorectal cancer

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Received May 28, 2018; Accepted August 23, 2018; Epub October 1, 2018; Published October 15, 2018

Abstract: Colorectal cancer (CRC) remains one of the leading causes of cancer-related deaths in the world. Chemotherapy has been used to treat CRC patients in order to improve prognosis. Oxaliplatin and 5-Fluorouracil (5-FU) based chemotherapy is a first line treatment for locally advanced and metastatic CRC. For patients with wild-type KRAS metastatic CRC, cetuximab (an EGFR monoclonal antibody) is a commonly used targeted therapy. CRC is initially sensitive to chemotherapy and targeted therapy. However, drug resistance frequently arises, which significantly affect the treatment outcome in these patients. An increasing number of studies have indicated that lncRNAs are implicated in the drug resistance of CRC. This review aims to gain insights into the role and molecular mechanism of lncRNAs in CRC drug resistance.

Keywords: CRC, lncRNA, drug resistance

Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer-related death worldwide [1]. In spite of recent developments in the treatment of the CRC, its prognosis is still unsatisfactory. Oxaliplatin and 5-Fluorouracil (5-FU)-based chemotherapy is a first line chemotherapy for locally advanced and metastatic CRC [2]. Oxaliplatin is a commonly used third-generation platinum analogue which kills tumor cells by forming an intrastrand linkage of two adjacent guanines on DNA [2]. Due to drug resistance, the response rate of oxaliplatin is only 50-60% in standard-of-care first-line therapy [3]. 5-FU is another base analogue used for CRC chemotherapy [4, 5]. However, 5-FU resistance is frequent in CRC patients, which impedes the clinical outcomes [6, 7]. For metastatic CRC with wild-type KRAS, the anti-epidermal-growth-factor-receptor (EGFR) monoclonal antibody, namely cetuximab, is commonly used [8]. When used alone, cetuximab elicits a durable response in 12-17% of CRC patients, and up to a 72% response rate is reached when combined with chemotherapy [8]. It has been identified that genetic mechanisms including KRAS,

NRAS, BRAF, PIK3CA and EGFR mutations are implicated in cetuximab resistance [9]. However, the role of non-genetic factors in cetuximab resistance is still unclear. Therefore, it is of great importance to investigate the mechanisms of drug resistance and identify the strategies to overcome drug resistance in CRC patients.

Molecular mechanisms of cancer cell drug resistance

Dysfunction of DNA damage repair

The DNA repair system is activated in normal cells when DNA damage is caused by various physical, chemical or biological factors, and the DNA damage can thus be efficiently repaired to sustain chromosome stabilization [10]. On the other hand, the dysfunctional activation of the DNA repair pathway frequently occurs in tumor cells. One of the molecular mechanisms for chemotherapy is to trigger DNA damage directly or indirectly, an action that eventually leads to cytotoxicity [11]. The tumor cells can become more tolerant to and even acquire resistance to chemotherapy when such DNA damage can be

lncRNAs and drug resistance in CRC

Table 1. lncRNAs and Colorectal cancer drug resistance

lncRNA	Key factors	Functions	References
lncRNA snaR		5-FU resistance	[49]
lncRNA UCA1	MiR-204-5p	5-FU resistance	[50]
lncRNA SLC25A25-AS1	EMT	5-FU resistance	[51]
Linc00152	MiR-139a-3p, ERBB4, AKT	Oxaliplatin resistance	[41]
LncRNA H19	Wnt/ β -catenin signaling	Methotrexate resistance	[62]
MALAT1	MiR-218, EZH2, EMT	Oxaliplatin resistance	[42]
lncRNA CRNDE	MiR-181a-5p, Wnt/ β -catenin signaling	5-FU resistance	[52]
lncRNA MEG3	Cell apoptosis	Oxaliplatin resistance	[43]
lncRNA PCAT-1	MDR, c-Myc	5-FU resistance	[53]
Linc00261		Cisplatin resistance	[44]
lncRNA PVT1		Cisplatin resistance	[45]
lncRNA MIR100HG	MiR-100, miR-125b, Wnt/ β -catenin signaling	Cetuximab resistance	[34]

repaired [12]. DNA is the key target of platinum/oxaliplatin, and tumor cells usually become resistant to platinum/oxaliplatin due to the abnormal activation of the DNA damage repair system. For example, it has been found that NF- κ B/HOTAIR is involved in chemoresistance by activating DNA damage repair signaling [13].

Alterations in drug efflux

The ATP binding cassette family in humans contains 49 known transporters which pump drugs out of cells [14, 15]. This will result in multidrug resistance (MDR) in tumor cells [16]. Among these proteins, adenosine triphosphate-binding cassette superfamily G member 2 (ABCG2), P glycoprotein (P-gp), and multi-drug resistant associate protein (MRP) have been widely explored in multiple tumors [16, 17].

Apoptosis

Two classic pathways are involved in cell apoptosis, the intrinsic pathway regulated by chondriosomes, and the extrinsic pathway regulated by tumor necrosis factor (TNF) receptors [18, 19]. The bcl-2 protein family contains both the apoptosis inducing proteins (Bax, Bad, and Bid) and the anti-apoptosis proteins (Bcl-2 and Bcl-xl) [20, 21]. These proteins antagonize each other to keep a balanced condition in the cells. Once the balance is disrupted, resistance to chemotherapy might arise.

Mutation of drug targets

Molecular targeted therapy is becoming a focus of cancer research because of fewer side

effects and high efficacy as compared with traditional chemotherapy [22, 23]. Resistance to these drugs might occur when the signaling pathways are altered or the molecular targets are mutated.

Long non-coding RNAs (lncRNAs) and CRC

In recent years, it has been reported that more than 90% of the human genome has been actively transcribed, yet less than 3% of the total human sequence encodes proteins, with the majority of the genome transcribed to produce non-coding RNAs (ncRNAs) [24]. lncRNAs are one group of the ncRNAs that are longer than 200 nucleotides with no protein coding potential [25]. lncRNAs play critical roles in multiple biological and pathological processes, including embryonic development, cell growth, cell apoptosis, cell migration, cell invasion, tumorigenesis, and metastasis, by acting as guides, scaffolds, tethers and decoys of other molecules [26-30].

Increasing evidence has demonstrated the important role of lncRNAs in the development, metastasis and prognosis of CRC. For example, Ling et al. reported that CCAT2 is a novel non-coding RNA that drives metastatic progression and chromosomal instability in colon cancer [31]; Ma et al. found that lncRNA CCAL regulates progression by activating the Wnt/ β -catenin signaling pathway via the suppression of activator protein 2 α in CRC [32]; Damas et al. demonstrated that SNHG5 promotes CRC cell survival by counteracting STAU1-mediated mRNA destabilization [33]. More recently, the

roles of lncRNA in drug resistance have attracted much attention. Lu et al. showed that lncRNA MIR100HG-derived miR-100 and miR-125b mediated cetuximab resistance via the Wnt/ β -catenin signaling. In this review, we focus on the role of lncRNAs on the drug resistance of CRC [34]. The lncRNAs that are associated with CRC drug resistance are listed in **Table 1**.

lncRNAs and oxaliplatin/cisplatin resistance

Oxaliplatin is a commonly used chemotherapy reagent for stage III and some stage II patients after surgery as well as metastatic patients [35, 36]. However, the frequent incidence of resistance to oxaliplatin impedes the treatment outcomes in these patients [37]. The underlying molecular mechanism of oxaliplatin resistance remains elusive. Previously, it has been reported that the extracellular signal-regulated kinase (ERK)/Extracellular signal-regulated kinase (MEK) pathway, the protein kinase B (AKT/PKB) pathway and the nuclear factor-kappa B (NF- κ B) pathway were involved in oxaliplatin resistance [38-40]. However, recent studies have shown that lncRNAs are involved in the regulation of oxaliplatin resistance. linc00152 functions as a ceRNA to confer oxaliplatin resistance via the miR-193a-3p/ERBB4/AKT signaling pathway. linc00152 antagonizes oxaliplatin-induced apoptosis in CRC cells; linc00152 could modulate the expression of ERBB4 by competing binding to miR-193a-3p [41]. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was first reported by Ji and colleagues as an oncogene in non-small cell lung cancer through the promotion of cell metastasis and invasion. MALAT1 is found to be overexpressed in CRC. A high expression of MALAT1 is associated with a poor response to oxaliplatin treatment in CRC patients. Further studies have indicated that MALAT1 tethers EZH2 to the CDH1 promoter and suppresses miR-218 expression during oxaliplatin treatment, which leads to CRC cell chemoresistance [42]. lncRNA MEG3 could promote chemosensitivity to oxaliplatin in CRC by enhancing oxaliplatin-induced cell cytotoxicity, and the down-regulation of lncRNA MEG3 indicates a poor therapeutic efficacy [43]. linc00261 is down-regulated in CRC cells, and the down-regulation of linc00261 is correlated with acquired cisplatin resistance, but the overexpression of linc00261 confers chemosensitivity. Further

investigation showed that linc00261 down-regulates β -catenin in nuclei and induces β -catenin degradation, inactivates the Wnt/ β -catenin pathway and downstream target genes, then inhibits TCF/LEF/ β -catenin complex formation, and finally, suppresses colon cancer and reduces the cisplatin resistance of tumor cells [44]. lncRNA PVT1 is up-regulated in CRC and positively associated with cisplatin-resistance in CRC. The knockdown of lncRNA PVT1 suppresses proliferation and induces apoptosis, thus enhancing cisplatin sensitivity in CRC cells. The molecular mechanism has revealed that lncRNA PVT1 promotes cisplatin resistance via the inhibition of the intrinsic apoptosis signaling pathway [45].

lncRNAs and 5-FU resistance

5-FU is a classical reagent for chemotherapy of CRC patients. However, the clinical application of 5-FU has been limited by its chemoresistance in many cases. Previous studies have showed some biomarkers can be used to predict sensitivity to 5-FU. For instance, it has been found that miR-204-5p enhances 5-FU sensitivity of CRC by downregulating RAB22A [46], and the polymorphisms of TS and MTHFR could predict the survival of gastric cancer patients treated with 5-FU based adjuvant chemotherapy in the Chinese population [47]. Lamas and colleagues reported a panel of biomarkers that is able to predict a response to a 5-FU/oxaliplatin regimen in patients with metastatic CRC [48]. However, there is still a need to explore the mechanism of 5-FU resistance in CRC. More and more results show that lncRNAs can regulate the 5-FU resistance in CRC. lncRNA snaR was down-regulated in 5-FU-resistant CRC cells, and lncRNA snaR loss increased cell viability after 5-FU treatment [49]. lncRNAUCA1 is up-regulated in CRC tissues and predicts a poor prognosis in CRC patients. Moreover, lncRNA UCA1 increases the 5-FU resistance in CRC cells. Further studies indicate that lncRNA UCA1 confers 5-FU resistance by regulating the miR-204-5p-CREB1/BCL2/RAB22A regulatory network [50]. The decreased expression of lncRNA SLC25A-AS1 induces chemoresistance to 5-FU and EMT in CRC cells by activating the Erk and P38 signaling pathways [51]. The lncRNA Colorectal Neoplasia Differentially Expressed (CRNDE) is transcribed from chromosome 16 on the strand opposite the adjacent

IRX5 gene. The expression of CRNDE was first found to be up-regulated in CRC. lncRNA CRNDE induces 5-FU resistance in CRC by acting as a ceRNA for miR-181a-5p. The knockdown of lncRNA CRNDE and the overexpression of miR-181a-5p inhibits cell proliferation and reduces chemoresistance. Moreover, the Wnt/ β -catenin signaling pathway is targeted by miR-181a-5p and lncRNA CRNDE regulates 5-FU resistance via the miR-181a-5p mediated regulation of Wnt/ β -catenin signaling. Taken together, lncRNA CRNDE could regulate the 5-FU chemoresistance of CRC by modulating the expression of miR-181a-5p and the Wnt/ β -catenin signaling pathway [52]. The lncRNA prostate cancer-associated ncRNA transcript 1 (PCAT-1) is associated with cell motility and the invasiveness of CRC cells, and the knockdown of PCAT-1 sensitizes CRC cells to 5-FU [53].

lncRNAs and cetuximab resistance

Cetuximab is an EGFR-directed monoclonal antibody which was approved to treat patients with metastatic CRC in 2004 [54, 55]. The efficacy of cetuximab is approximately 10% when used as monotherapy for oxaliplatin-refractory and/or irinotecan-refractory metastatic CRC [56]. Previous studies have indicated that some genetic or pathway alterations are partly to account for the resistance of cetuximab in CRC: the mutations disrupting the binding of cetuximab to EGFR, the mutations of the downstream pathway (KRAS or BRAF mutation), and the activation of the parallel pathway (such as MET and ERBB2) [56-60]. However, the genetic mechanisms do not account for all the patients who are clinically resistant to cetuximab therapy. In a recent study, Lu and colleagues found that lncRNA MIR100HG and two embedded miRNAs, miR-100 and miR-125b, are associated with cetuximab resistance in CRC cells [34]. They showed that lncRNA MIR100HG and miR-100/125b are up-regulated in cetuximab-resistant cells and head and neck squamous cell cancer as well as in tumors from CRC patients that progressed on cetuximab. miR-100 and miR-125b coordinately inhibited the Wnt/ β -catenin signaling negative regulators (DKK1, DKK3, ZNRF3, RNF43, APC2), leading to the activation of Wnt/ β -catenin signaling. Inhibition of the Wnt/ β -catenin signaling could restore the responsiveness to cetuximab in cetuximab-resistant CRC cells [34]. In addition, the overex-

pression of lncRNA MIR100HG was reinforced by the miR-125b suppression of GATA6 [34].

Other drugs related to lncRNAs

Some other drug resistance was also found to be associated with lncRNAs. The vitamin D receptor (VDR) signaling inhibits the expression of lncRNA H19 via the C-myc/Mad-1 axis, and lncRNA H19 suppresses the expression of VDR by way of miR-675-5p. Moreover, lncRNA H19 overexpression resulted in resistance to 1,25(OH)₂D₃ treatment in CRC cells [61]. In another study, Wu and colleagues found lncRNA H19 was significantly up-regulated in a methotrexate (MTX) resistant CRC cell. The knockdown of lncRNA H19 sensitized MTX resistance in CRC cells, but the overexpression of lncRNA H19 increased MTX resistance in CRC cells. Further investigation showed that the Wnt/ β -catenin signaling was activated by the overexpression of lncRNA H19. In conclusion, lncRNA H19 mediated MTX resistance by activating the Wnt/ β -catenin signaling pathway [62].

Conclusion

Increasing evidence indicates that lncRNA dysfunction is involved in the pathological processes and prognosis of CRC, including lymph node invasion, distant metastasis, and poor prognosis [26, 63-66]. lncRNAs have also been found to be associated with drug resistance in various tumor types, such as bladder cancer, ovarian cancer, gastric cancer, non-small cell lung cancer and CRC [67-70]. In spite of the progress in the treatment of CRC in the past decades, the prognosis of CRC is still poor, especially in patients with metastatic CRC. One of the reasons for the poor prognosis is the drug resistance [18]. It is of great importance to identify the factors and the underlying molecular mechanisms of drug resistance. Oxaliplatin and 5-FU are the most commonly used chemotherapy regimen for adjuvant chemotherapy and palliative chemotherapy for CRC patients. The anti-EGFR monoclonal antibody cetuximab is used for metastatic CRC only.

It has been reported that the mechanism of drug resistance is very complicated. Different patients might develop drug resistance in different ways. The apoptosis signaling pathway is involved in oxaliplatin resistance. The CREB1/BCL2/RAB22A regulatory network is involved in

5-FU resistance. Interestingly, the Wnt/ β -catenin signaling is involved in the resistance of oxaliplatin, 5-FU and cetuximab. This indicates that blocking the Wnt/ β -catenin signaling may be a promising way to overcome drug resistance.

In conclusion, drug resistance is an obstacle in the clinical treatment of CRC. Research on the association and drug resistance in CRC has attracted more and more attention. Many lncRNAs have been proved to be associated with drug resistance in CRC. Further studies are needed to investigate a way to improve the responsiveness of drugs. The exploration of the relationship between lncRNAs and CRC might shed more light on the prediction of prognosis and options of drugs in these patients.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (no. 81372570; No 81602053), the Natural Science Foundation of Guangdong Province (no. 2014A030312015; no. 2016A030310195), the Science and Technology Program of Guangdong (no. 2015B020232008), the Science and Technology Program of Guangzhou (nos. 155-70006 and 158100066), and the fourth outstanding young talents training plan of Sun Yat-sen University Cancer Center (no. PT04141001).

Disclosure of conflict of interest

None.

Abbreviations

lncRNAs, long non-coding RNAs; EGFR, epidermal growth factor receptor; MDR, multidrug resistance; P-gp, P glycoprotein; ABCG2, Adenosine triphosphate-binding cassette superfamily G member 2; 5-FU, 5-fluorouracil; CRC, colorectal cancer; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MTX, methotrexate; MRP, multi-drug resistant associate protein.

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