Navigating the labyrinth of long non-coding RNAs in colorectal cancer: From chemoresistance to autophagy

Yu JM et al. LncRNAs regulate autophagy and chemoresistance

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Abstract
Long non-coding RNAs (IncRNAs), with transcript lengths exceeding 200 nucleotides and little or no protein-coding capacity, have been found to impact colorectal cancer (CRC) through various biological processes. LncRNA expression can regulate autophagy, which plays dual roles in the initiation and progression of cancers, including CRC. Abnormal expression of IncRNAs is associated with the emergence of chemoresistance. Moreover, it has been confirmed that targeting autophagy through IncRNA regulation could be a viable approach for combating chemoresistance. Two recent studies titled “Human β-defensin-1 affects the mammalian target of rapamycin pathway and autophagy in colon cancer cells through long non-coding RNA TCONS_00014506” and “Upregulated IncRNA PRNT promotes progression and oxaliplatin resistance of colorectal cancer cells by regulating HIPK2 transcription” revealed novel insights into IncRNAs associated with autophagy and oxaliplatin resistance in CRC, respectively. In this editorial, we particularly focus on the regulatory role of IncRNAs in CRC-related autophagy and chemoresistance since the regulation of chemotherapeutic sensitivity by intervening with the IncRNAs involved in the autophagy process has become a promising new approach for cancer treatment.

Key Words: Long non-coding RNA; Autophagy; Chemoresistance; Oxaliplatin; Colorectal cancer

**Core Tip:** Long non-coding RNAs (lncRNAs) expression can regulate both autophagy and chemoresistance in colorectal cancer (CRC). Autophagy exerts dual effects on chemotherapy resistance through multiple mechanisms, including the regulation of autophagy-related lncRNAs. In this editorial, we focus on the role of lncRNAs in the regulation of autophagy and chemoresistance in CRC and explore the feasibility of modulating chemosensitivity by interfering with lncRNAs involved in the autophagic process.

## INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related death worldwide\(^1\). It is paramount to extensively and intensively investigate the pathogenesis of CRC to facilitate the development of effective therapeutic strategies. Two recent studies by Li *et al*\(^2\) and Zhao *et al*\(^3\) have provided fresh perspectives on the molecular intricacies of CRC and presented novel therapeutic targets. Li *et al*\(^2\) focused on the long non-coding RNAs (lncRNA) PRNT/ZNF184/HIPK2 axis and its role in oxaliplatin resistance, while Zhao *et al*\(^3\) investigated the influence of human β-defensin-1 on autophagy through the lncRNA TCONS_00014506.

LncRNAs are implicated in the onset and progression of various human malignancies, including CRC\(^4\). These molecules can interact with RNA-binding proteins and act as competing endogenous RNAs (ceRNAs) for microRNAs (miRNAs), which are involved in epigenetic modification of DNA and RNA, thereby affecting the expression of relevant genes. These lncRNA-mediated changes can induce or inhibit autophagy in tumour cells and mediate drug resistance\(^4-6\).

Autophagy is a cellular process in which components such as proteins and organelles are transported to lysosomes for degradation\(^7\). Previous studies have shown that autophagy plays dual roles in tumorigenesis\(^8\). On the one hand, the
expression of IncRNAs has been shown to regulate autophagy in CRC, and on the other hand, IncRNAs and autophagy have cross-regulatory and dual effects on tumours: IncRNAs can increase or decrease autophagy, and changes in autophagy can further promote or inhibit tumour growth[6].

Chemotherapy is essential for patients with locally advanced or metastatic CRC[9]. Oxaliplatin-based chemotherapy has been used worldwide as a first-line treatment for CRC[10]. However, the prognosis of CRC patients is not as satisfactory as expected. Endogenous and acquired oxaliplatin resistance is now considered a major obstacle limiting treatment success[11]. Studies have shown that IncRNAs are key factors in oxaliplatin resistance, and their dysregulation induces the activation of several signalling pathways, which ultimately leads to chemoresistance[12].

Autophagy also plays dual roles in the development of chemotherapeutic resistance, either by promoting or inhibiting resistance through many complex mechanisms, including the regulation of autophagy-related IncRNAs (ARlncRNAs)[6]. In this editorial, we focus on the role of IncRNAs in the regulation of autophagy and chemoresistance in CRC and explore the feasibility of modulating chemosensitivity by interfering with IncRNAs involved in the autphagic process.

LNCRNAs REGULATE AUTOPHAGY IN CRC

The effects of IncRNAs on autophagy and the influence of IncRNA-regulated autophagy on CRC pathogenesis are complicated[13]. Inhibition of autophagy by lincPOU3F3 in LOVO and SW480 CRC cells may enhance the malignant phenotype of CRC[14]. Similarly, the inhibition of LINC00858 induces colon cancer cell apoptosis, senescence, and autophagy. LINC00858 functions as a tumour-promoting IncRNA in colon cancer through the downregulation of WNK2[15]. Moreover, the IncRNA CPS1IT might suppress metastasis and EMT by inhibiting hypoxia-induced autophagy through the inactivation of HIF-1α in CRC[16]. In addition, the IncRNAs SLCO4A1-AS1[17], UCA1[18], and MALAT1[19] promote autophagy through the miRNA-related axis, thus enhancing the proliferation of CRC cells. The dual regulatory role of ARlncRNAs, determined by the dual nature of autophagy, can serve as an effective therapeutic target for CRC[20].
Human β-defensin 1 (hBD-1) is a multifaceted antimicrobial peptide that acts as a tumour suppressor\textsuperscript{[21]} . Zhao \textit{et al}\textsuperscript{[19]} verified that hBD-1 may induce autophagy in colon cancer SW620 cells by inhibiting the phosphorylation of mTOR through the IncRNA TCONS_00014506 at the cellular level. However, this study focused on a single cell line, and the impact of hBD-1 was not assessed; this is a limitation that could be addressed in future research. Moreover, an investigation of the expression and function of TCONS_00014506 in patient-derived tumour samples could provide clinically relevant support for the \textit{in vitro} findings. Bioinformatics analysis of autophagy-related differentially expressed IncRNAs was performed to offer novel insights on strategies that could complement existing treatments to potentially overcome resistance mechanisms and improve patient outcomes.

\textbf{LncRNAs Regulate Oxaliplatin Resistance in CRC}

In recent years, emerging evidence has shown that IncRNAs play irreplaceable roles in drug resistance\textsuperscript{[4,6,21]} . However, we have limited knowledge of the IncRNAs that are closely related to oxaliplatin resistance in CRC. A novel IncRNA, Lnc00152 antagonizes oxaliplatin sensitivity by acting as a competing ceRNA to modulate the expression of miR-193a-3p and subsequently modulate the expression of erb-b2 receptor tyrosine kinase 4\textsuperscript{[22]} . The IncRNAs CACS15\textsuperscript{[24]} , KCNQ1OT1\textsuperscript{[25]} , MEG3\textsuperscript{[26]} , CRNDE\textsuperscript{[27]} , LINC00525\textsuperscript{[28]} , and MALAT1\textsuperscript{[29,30]} promote oxaliplatin resistance by sponging specific miRNAs. In addition, the IncRNA CCAL facilitates resistance to oxaliplatin in CRC cells by increasing the level of β-catenin expression\textsuperscript{[31]} . The IncRNA LUCAT1 affects oxaliplatin sensitivity through the p53 signalling pathway. Knockdown of LUCAT1 renders CRC cells hypersensitive to oxaliplatin treatment\textsuperscript{[32]}.

A recent study by Li \textit{et al}\textsuperscript{[2]} revealed that the IncRNA PRNT is upregulated in oxaliplatin-resistant CRC cells and modulates the expression of HIPK2 by sponging ZNF184, marring bioinformatics analyses with robust \textit{in vitro} and \textit{in vivo} experiments. However, there is a pressing need to validate the clinical relevance of the PRNT/ZNF184/HIPK2 axis in a larger cohort of CRC patients. Considering the role of PRNT in chemoresistance, a systematic characterization of IncRNAs may
redefine our approach to cancer treatment. Furthermore, examining the interplay between IncRNAs and other signalling pathways could uncover additional layers of regulation and points of intervention.

**AUTOPHAGY-RELATED LNCRNAS REGULATE CHEMORESISTANCE IN CRC**

ARlncRNAs can mediate both sides of autophagy and thus can positively or negatively affect drug resistance\(^{[20]}\). Autophagy-mediated drug resistance is a complex phenomenon involving multiple factors, including the recirculation of cytoplasmic components, gene repair mechanisms, alterations in drug concentration and metabolism, changes in the expression or activity of key proteins, and modifications in apoptotic and survival signalling pathways\(^{[6]}\).

LncRNA H19 promotes SIRT1-dependent autophagy via miR-194-5p, thereby inducing 5-FU resistance in CRC\(^{[33]}\). The knockdown of NEAT1 attenuates autophagy by targeting miR-34a to increase 5-FU sensitivity\(^{[34]}\). SNHG6 may promote chemoresistance through ULK1-induced autophagy by sponging miR-26a-5p in CRC cells\(^{[35]}\). In vivo and in vitro, the IncRNA UCA1 promotes autophagy through the miR-23b-3p/ZNF281 axis, which mediates resistance to 5-FU in CRC cells\(^{[36]}\). Similarly, the IncRNA SNHG14 stimulates cellular autophagy through interaction with the miR-186/ATG14 axis to promote cisplatin resistance in CRC\(^{[37]}\).

The IncRNA TUG1 targets miR-195-5p and blocks its expression. MiR-195-5p promotes the HDGF/DDX/β-catenin axis, thereby triggering autophagy, which promotes resistance to cisplatin\(^{[38]}\).

Both recent studies are noteworthy, as they revealed the roles of IncRNAs in CRC progression and treatment resistance. A more comprehensive approach is necessary to elucidate the network of IncRNA interactions in CRC since they focused on individual IncRNAs. ARlncRNAs act by regulating specific downstream miRNAs\(^{[20]}\). However, individual IncRNAs can regulate more than one miRNA, so broader exploration of the numerous targets or signalling pathways downstream of ARlncRNAs is essential. Furthermore, the interaction between autophagy and
chemoresistance remains an underexplored topic, and studies in this area may reveal innovative CRC therapies.

**CONCLUSION**
Although modulating chemosensitivity by interfering with lncRNAs involved in the autophagy process is a promising new approach for cancer treatment, multicentre validations based on sufficient samples are still necessary. With our increasing knowledge of lncRNAs in CRC, there is promise that some lncRNAs might be applied in biomarker-directed precision medicine approaches to improve survival outcomes in CRC patients.

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**Figure 1 Mutual relationship between long non-coding RNAs, autophagy, and chemoresistance.** A: Long non-coding RNAs (LncRNAs) can promote (blue line) or inhibit (orange line) autophagy and chemoresistance. Autophagy-related LncRNAs can positively or negatively influence drug resistance; B: LncRNAs function as competing endogenous RNAs by binding to specific microRNAs, leading to the
activation of autophagy and ultimately enhancing resistance to 5-FU, cisplatin, and oxaliplatin. IncRNA: Long non-coding RNAs.
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