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Emerging roles of non-coding RNAs in colorectal cancer oxaliplatin resistance and liquid biopsy potential

Roles of ncRNAs in oxaliplatin resistance

Abstract

Colorectal cancer (CRC) is one of the most common malignancies of the digestive tract, with annual incidence and mortality increasing consistently. Oxaliplatin-based chemotherapy is a preferred therapeutic regimen for patients with advanced CRC. However, most patients will inevitably develop resistance to oxaliplatin. Many studies have reported that non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are extensively involved in cancer progression. Moreover, emerging evidence has revealed that ncRNAs mediate chemoresistance to oxaliplatin by transcriptional and post-transcriptional regulation, in addition to by epigenetic modification. In this review, we summarise the mechanisms by which ncRNAs regulate the initiation and development of CRC chemoresistance to oxaliplatin. Furthermore, we investigate the clinical application of ncRNAs as promising biomarkers for liquid CRC biopsy. This review provides new insights into overcoming oxaliplatin resistance of CRC by targeting ncRNAs.

Key Words: Colorectal cancer; Non-coding RNAs; Oxaliplatin; Resistance; Liquid biopsy biomarkers

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Core Tip: Oxaliplatin has served as a first-line chemotherapy option for Colorectal cancer (CRC). However, owing to congenital or acquired resistance, treatment failure is common in some patients with CRC. Abundant evidence has discovered that non-coding RNAs (ncRNAs) are extensively involved in cancer progression, including drug resistance. Specifically, ncRNAs mediate resistance to oxaliplatin by mediating drug carriers, tumor microenvironment, resistance-related signaling pathways, and patterns

of cell death. Importantly, we investigated the potential and clinical application values of these ncRNAs as liquid biopsy markers for CRC.

INTRODUCTION

Colorectal cancer (CRC) is considered to be the leading cause of malignancy death associated with the gastrointestinal tract, with approximately 1,932 million new cases and 935,000 deaths in 2020 [1]. Currently, surgery is the preferable treatment option for early CRC patients, however, it has few clinical benefits for advanced patients due to high rates of postoperative metastasis and recurrence [2, 3]. The annual survival rate for stage III CRC patients is about 30%-60%; this figure drops to just 10% for stage IV patients [4, 5]. The combination of oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) has significantly increased the overall survival (OS) of patients and now serves as a first-line standard regimen for metastatic CRC (mCRC) [6]. Oxaliplatin is a widely used third-generation platinum analog that functions by reacting with DNA to form hydration derivatives with intra- and inter-strand crosslinks eventually resulting in cell death [7]. However, oxaliplatin has not been satisfactory in improving the survival rate of some patients due to drug resistance [8]. Moreover, some toxic side effects persist after oxaliplatin treatment; these include peripheral neurotoxicity, which further hinders the chemotherapy [9]. Fortunately, oxaliplatin-based chemotherapy retreatment strategies are being optimized to provide further personalized therapy for patients with mCRC [10]. Therefore, it is of great importance to understand the mechanism by which oxaliplatin resistance manifests, and to identify new biomarkers that can aid prediction of the outcomes for CRC patients treated with oxaliplatin-based therapy.

Although the processes of chemoresistance in CRC are intricate and inconclusive [11], ongoing research has revealed multiple oxaliplatin resistance mechanisms. Several studies have confirmed that chemoresistance is associated with the dysregulation of efflux proteins and drug-metabolizing enzymes, such as ABC transporters and GSTP1; these enzymes mediate drug uptake, transport, and toxicity [12, 13]. Furthermore, accumulating evidence suggests that epithelial-mesenchymal transition (EMT) [14] and

DNA damage repair [15] are driving factors that result in chemoresistance and tumor progression. Many studies have reported that various signaling pathways, such as the TGF-β/Smad [16], JNK/p38 MAPK [17], Wnt/β-catenin [18], and MEK/ERK/ELK1 [19] pathways are closely associated with oxaliplatin resistance. As the main regulatory components of the tumor microenvironment (TME), cancer-associated fibroblasts (CAFs) [20] and tumor-associated macrophages (TAMs) [21] can modulate cancer chemotherapy resistance through complex mechanisms of crosstalk. Of note, emerging studies have confirmed that cell death mechanisms play a pivotal role in chemoresistance. It has been reported that apoptosis inhibition [22] and autophagy dysregulation [23] are underlying mechanisms leading to chemoresistance. Furthermore, abundant studies have identified that several additional death mechanisms can mediate CRC chemoresistances, including ferroptosis [24], pyroptosis [25], necroptosis [26], and others. However, the detailed molecular mechanisms by which these cell death modes lead to oxaliplatin resistance are unclear and require further investigation.

Non-coding RNAs (ncRNAs) refer to RNA molecules transcribed from genes that cannot encode proteins, accounting for more than 90% of human gene transcripts. ncRNAs can be divided into either small ncRNAs (< 200 nucleotides) or long non-coding RNAs (lncRNAs) (> 200 nucleotides) based on their length [27-29]. In the last decade, circRNAs, a type of circular RNA generated in the splicing process of pre-mRNA, have emerged as a focus of research [30] (Figure 1). A growing number of studies have revealed that ncRNAs play critical roles in the occurrence and development of multiple human diseases *via* various mechanisms, such as epigenetics, transcription, and post-transcriptional [31, 32]. Moreover, microRNA (miRNAs), lncRNAs, and circRNAs are three of the more widely studied types of ncRNAs and have been shown to mediate tumor progression by regulating tumor cell proliferation, aggression, metastasis, apoptosis, and drug resistance, amongst other pathways [33, 34]. Drug resistance is one of the key factors for malignancy treatment failure, whether this is mediated by ncRNAs has attracted increasing attention. In recent years, the rapid development of next-generation sequencing (NGS) technologies has expanded the

understanding of tumor pathogenesis and drug resistance mechanisms, and an increasing number of tumor chemoresistance-associated differential ncRNAs have been identified [35-37]; these developments have provided the expansion of open datasets of candidate ncRNAs for basic research and clinical application. Currently, the targeting of ncRNAs as biomarkers in the clinic is being actively facilitated [38]. As such, a systematic understanding of the underlying roles of ncRNAs in malignancies provides valuable insights into overcoming chemoresistance in CRC patients.

Although tissue biopsy is the gold standard for malignancy diagnosis, the availability of clinical samples is often limited, and subsequently, tumor heterogeneity may not be reflected in analysis and is therefore not suitable for longitudinal clinical monitoring [39]. As a noninvasive approach, liquid biopsy has been extensively applied for the real-time monitoring of variations in tumor dynamics in body fluids including blood, ascites, and others. With the development of novel molecular detection technologies, growing evidence suggests that circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating free nucleic acids (cfDNA and cfRNA), tumor-educated platelet (TEP), exosomes, etc [40, 41]; these cellular markers have gradually become prominent liquid biopsy hallmarks. Owing to their stability and high abundance, circulating ncRNAs can provide substantial details regarding tumor biology and therapeutic efficacy, and have become candidate biomarkers for earlier diagnosis, therapeutic monitoring, and prognosis evaluation of malignancies [42, 43].

In this study, we performed a systematic literature review to identify the latent mechanisms of ncRNAs (miRNAs, lncRNAs, and circRNAs) in CRC oxaliplatin resistance. In particular, exosomal ncRNAs, as one of the most promising biomarkers in liquid biopsies, are expected to improve diagnostic, therapeutic, and drug monitoring in CRC patients.

OVERVIEW OF THE REGULATORY ROLES OF NCRNAS IN CRC OXALIPLATIN RESISTANCE

Classification and biological functions of miRNAs

MiRNAs are a class of small ncRNAs of approximately 22 nucleotides in length; they are produced by two RNase III proteins, Drosha and Dicer [44]. In general, miRNAs bind to the 3' untranslated region (UTR) of their target mRNAs resulting in cleavage or translational repression in the cytosol [45]. Intriguingly, numerous recent studies have demonstrated that some miRNAs activate gene transcription unconventionally in the nucleus by targeting enhancers, such miRNAs are known as nuclear activating miRNAs (NamiRNAs) [46]. Moreover, enhancers (including super-enhancers) have been revealed to synergistically promote NamiRNA biogenesis and activate the expression of proximal genes [47, 48]. Further studies have reported that the dysregulation of microRNAs may play an important role in CRC oxaliplatin resistance, as we illustrate in Table 1.

Oncogenic miRNAs mediate the oxaliplatin resistance in CRC

MiR-135b-5p has been confirmed to be upregulated in the serum of CRC patients, mechanistically this has been shown to induce protective autophagy *via* the MUL1/ULK1 signaling pathway, a process that contributes to oxaliplatin resistance [49]. Another miRNA, miR-454-3p, is highly expressed in oxaliplatin-resistant CRC cells compared to in oxaliplatin-sensitive cells and promoted oxaliplatin resistance *via* inhibiting PTEN expression and activation of the AKT pathway [50]. Similarly, targeting miR-19a with high expression in oxaliplatin-resistant CRC cell lines could promote oxaliplatin sensitization of resistant cells through activation of the PTEN/PI3K/AKT pathway [51]. Compounding these findings, it has been revealed that dichloroacetate (DCA), a pyruvate dehydrogenase kinase (PDK) inhibitor, can enhance the chemosensitivity of oxaliplatin-resistant CRC cells through the miR-543/PTEN/Akt/mTOR pathway and the miR-107/CAB39/AMPK/mTOR pathway [52, 53]. Besides, an unbiased microRNA array demonstrated that miR-503-5p was up-regulated in oxaliplatin-resistant CRC cells; overexpression of miR-503-5p conferred resistance to oxaliplatin-induced apoptosis by inhibiting PUMA expression [54]. Further studies have revealed that by targeting BNI1, up-regulation of miR-744 enhanced the resistance of T84 and HCT116 cells to oxaliplatin [55]. Moreover, the oncogenic miR-

5000-3p was upregulated in CRC tissues and oxaliplatin-resistant CRC cells, this miRNA negatively regulated USP9 to facilitate CRC chemoresistance [56]. Additionally, natural killer (NK) cells contributed to enhancing the sensitivity of oxaliplatin resistance CRC cells through the microRNA-146b-5p/WBSCR22 axis [57]. Remarkably, miR-19b-3p has been documented to be the most significantly upregulated candidate miRNA in colon cancer tissues, its expression correlates with tumorous histologic grading, staging, and poor prognosis in patients. Importantly, miR-19b-3p facilitated proliferation, curbed apoptosis, and induced oxaliplatin resistance in CRC cells by targeting SMAD4 [58].

Tumor-suppressive miRNAs mediate the oxaliplatin resistance in CRC

Interestingly, it has been demonstrated by some that tumor-suppressive miRNAs are associated with oxaliplatin resistance. Studies have identified that miR-1278 was significantly downregulated in CRC tissues, and that overexpression of miR-1278 inhibited CRC progression and enhanced oxaliplatin sensitivity through targeting of the KIF5B/BTG2 axis [59]. Similarly, miR-506 was weakly expressed in chemoresistant CRC cells, but its overexpression has been confirmed to restore the resistance of HCT116 cells to oxaliplatin *via* the Wnt/β-catenin pathway [60]. Moreover, miR-200b-3p was down-regulated in oxaliplatin-resistant CRC tissues and cells (HT29-OR and HCT116-OR), and studies revealed that miR-200b-3p reversed oxaliplatin resistance of CRC cells *via* the targeting of TUBB3 [61]. Furthermore, MiR-122, which was down-regulated in oxaliplatin-resistant SW480 and HT29 cells, has been demonstrated to be overexpressed in CRC cells, this could enhance the chemosensitivity of CRC by inhibiting the expression of XIAP [62]. As a tumor suppressor, miR-193a-5p can act directly upon CXCR4 to mitigate the chemosensitivity of CRC cells to 5-FU and oxaliplatin [63]. Using sequencing, Liang *et al* [64] discovered that miR-483-3p was negatively correlated with FAM171B expression, and targeting the miR-483-3p/FAM171B regulatory axis could enhance the sensitivity of CRC cells to oxaliplatin. Moreover, miR-325 mimics were observed to prevent the development of oxaliplatin resistance in CRC *via* interference with the HSPA12B/PI3K/AKT/Bcl-2 axis [65]. Finally, a proteomic analysis study

reported that regulation of miR-195-5p and miR-497-5p is a potential strategy for alleviating oxaliplatin resistance in CRC cells [66].

As an additional factor, several groups exhibited that the interaction between ncRNAs and autophagy exerted significant roles in the therapeutic resistance of CRC [67]. Sun *et al* [68] demonstrated that miR-34a was expressed at low levels in oxaliplatin-resistant CRC patients and cells. Overexpression of miR-34a contributed to facilitating the sensitivity of CRC cells to oxaliplatin *via* regulating the TGF-β/Smad4 pathway resulting in the inhibition of macroautophagy [68]. Furthermore, c-Myc has been shown to promote oxaliplatin resistance in CRC by integrating into the miR-27B promoter region and further mediating activation of the miR-27b-3p/ATG10 axis [69].

It is noteworthy that miR-181a could suppress the expression of BIRC6, a protein inhibitor of apoptosis, by directly targeting the 3'-UTR of BIRC6 mRNA [70]. Conversely, BIRC6 was observed to be significantly upregulated in acquired oxaliplatin-resistant CRC cells when compared to parental cells [71]. Considering that knockdown of BIRC6 helped enhance the chemosensitivity of CRC cells to oxaliplatin, targeting BIRC6 using miR-181a mimics may be a potential strategy to reverse oxaliplatin resistance in CRC.

Classification and biological functions of lncRNAs

LncRNAs are defined as a class of ncRNA molecules with transcript lengths of more than 200 nucleotides; they do not encode proteins due to their lack of an open reading frame [72]. LncRNAs can be classified into intergenic, intronic, sense, antisense, and bidirectional lncRNAs based on their genomic localization [73]. Alternatively, there are four categories of lncRNAs based on their functional mechanisms, including signal, decoy, guide, and scaffold lncRNAs [74, 75]. It has been reported that LncRNAs can regulate transcription, translation, RNA stability, and alternative splicing [76-79]. It is noteworthy that numerous studies have revealed that aberrant lncRNAs (oncogenic and tumor suppressive lncRNAs) contribute to regulating the mechanism of oxaliplatin resistance through multiple cellular mechanisms, including but not limited to DNA damage repair, interference with drug influx and efflux, regulation of cell cycle and apoptosis and activation of signaling pathways [80, 81]. Table 2 provides an overview of

some aberrant lncRNAs and their target molecules in the context of oxaliplatin resistance in CRC.

Oncogenic lncRNAs as regulators of CRC oxaliplatin resistance

Studies discovered that high expression of the lncRNA GIHCG promoted the proliferation, migration, and invasion of tumor cells, and enhanced their resistance to 5-FU and oxaliplatin [82]. Similarly, overexpression of the lncRNA ARSR reduced cell apoptosis and induced oxaliplatin resistance [83]. Notably, emerging evidence has revealed that lncRNAs could target mRNAs to promote chemoresistance [84]. For instance, upregulation of the lncRNA HOTAIR has been reported to facilitate EMT in a ZEB1-dependent manner by negatively regulating miR-1277-5p, a process that is involved in hypoxia-indued oxaliplatin resistance [85]. We previously discovered that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was overexpressed in CRC tissues compared to paired noncancerous tissues. Correspondingly, the overexpression of MALAT1 suppressed E-cadherin expression and promoted oxaliplatin-induced EMT by interacting with EZH2. Furthermore, upregulated MALAT1 further inhibited miR-218 expression, resulting in poor response to oxaliplatin-based chemotherapy in CRC patients [86]. Abundant studies have demonstrated that some endogenous transcripts (such as endogenous pseudogenes, lncRNAs, and circRNAs) can complement miRNAs in sequences and inhibit their expression, resulting in the upregulation of target gene expression. This phenomenon is called the miRNA "sponge" effect [87]. Analogously, Fan *et al* [88] demonstrated that MALAT1 could function as a "sponge" for miR-324-3p and increase the expression of ADAM17 to facilitate resistance to oxaliplatin in CRC cells.

Moreover, lncRNA Opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) can complement the sites of miR-137 in sequence, sponging miR-137 and inhibiting its expression, thus conferring oxaliplatin resistance to CRC cells [89]. It was reported that Linc00152 increased ERB-B2 receptor tyrosine kinase 4 (ERBB4) expression through acting as a "sponge" for miR-193a-3p resulting in the promoted phosphorylation of AKT at Thr308 and Ser47; this process mediated oxaliplatin resistance in CRC cells [90].

In addition, researchers have illustrated that the lncRNA MIR155HG promoted M2 macrophage polarization and enhanced oxaliplatin resistance in CRC cells by regulating the miR-650/Annexin A2 axis [91]. Similarly, other lncRNAs such as CASC15 [92], CBR3-AS1 [93], CRNDE [94], LINC00460 [95], and KCNQ1OT1 [96] have been reported to serve as "sponges" for miRNAs, thereby mediating oxaliplatin resistance in CRC.

Several research groups have revealed that lncRNAs could stabilize functional proteins, and mediate the chemoresistance of cancers. For example, lncRNA-RP11-536 K7.3 contributed to oxaliplatin resistance by recruiting SOX2 to activate deubiquitinase USP7 and stabilize the protein HIF-1α in CRC cells [97]. Furthermore, the lncRNA TUG1 induced oxaliplatin resistance in CRC stem cells and inhibited cell apoptosis *via* interacting with GATA6 [98]. Moreover, two additional studies have further revealed that the lncRNAs LUCAT1 and PiHL mediated oxaliplatin resistance in CRC cells by interacting with UBA52 and EZH2 proteins, respectively [99, 100].

LncRNAs have also been demonstrated as regulators of gene expression by their enhancing the stability of mRNA through epigenetic mechanisms [101]. Studies have elucidated that the lncRNA ELFN1-AS1 suppressed myeloid ecotype virus insertion site 1 (MEIS1) transcription and promoted oxaliplatin resistance *via* interacting with EZH2 and DNA methyltransferase 3 alpha (DNMT3a) after localization to the promoter region of MEIS1 gene [102]. Besides, overexpression of the lncRNA SNHG 5 contributed to the proliferation of CRC cells and their resistance to oxaliplatin-induced apoptosis *via* blocking the degradation of SPATS 2 by STAU 1 [103]. Of note, it has been identified that in microsatellite stable CRC, overexpression of the lncRNA CCAT2 could induce chromosomal instability (CIN), and enhance 5-FU and oxaliplatin-resistance by the upregulation of ribosomal biogenesis factor (BOP1) and the activation of aurora kinase A (AURKA) [104].

Tumor-suppressive lncRNAs as regulators of CRC oxaliplatin resistance

Previously, several tumor suppressor lncRNAs have been reported to be associated with CRC oxaliplatin resistance. For instance, the expression levels of NBAT-1 and MEG3 in CRC tissues were low compared with normal adjacent tissues, especially in

oxaliplatin-resistant patients [105, 106]. Mechanistically, NBAT-1 was revealed to inhibit the growth of oxaliplatin-resistant CRC cells by activating the WWC 3/LATS 1/YAP pathway after acting as a "sponge" for miR-454 [105]. Similarly, MEG3 promoted the sensitivity of CRC cells to oxaliplatin by regulating the miR-141/PDCD4 axis [107]. It has further been reported that lnc-AP is a lncRNA with coding potential, and is highly associated with oxaliplatin resistance in CRC; lnc-AP encodes the short peptide pep-AP that enhances sensitization of CRC cells to oxaliplatin *via* the pep-AP/TALDO1 pathway [108]. Intriguingly, an epidemiological investigation demonstrated that an rs2278176 CT/TT mutation in the lncRNA PVT1 increased the chemosensitivity of CRC patients to FOLFOX compared to CRC patients carrying distinct genotypes [109].

Of note, when compared to parental cells, the lncRNA CRNDE was significantly down-regulated in oxaliplatin-resistant cells and can be considered a predictor of oxaliplatin treatment response and tumor prognosis [110]. Interestingly, this lncRNA can be combined with arginine-rich splicing factor 6 (SRSF6) to reduce its stability, knockdown of the latter can inhibit autophagy and increase the sensitivity of cancer cells to oxaliplatin by the alternative splicing of PICALM [111]. Given that up-regulated expression of CRNDE aids an increase in the sensitivity of cancer cells to oxaliplatin, we speculate that increasing CRNDE expression and decreasing the stability of SRSF6 may be a promising strategy to ameliorate CRC resistance to oxaliplatin.

Classification and biological functions of circRNAs

Most circRNAs consist of covalently closed loop single-stranded RNAs produced by the back-splicing of exon precursor mRNAs that are more stable than their linear precursor gene [30]. Currently, circRNAs consist of four general categories: exonic circRNAs (EcircRNAs), circular intronic RNAs (CiRNAs), exon-intron circRNAs (EIciRNAs), and circRNA from other sources (Such as antisense circular RNA or intergenic circular) based on their structural domains and biogenesis features [112, 113]. As vital biological regulators, circRNAs have been reported to widely participate in multiple oxaliplatin resistance-related mechanisms, such as apoptosis, autophagy, glycolysis, TME, EMT, DNA damage repair, etc [114]. Studies identified that

hsa_circ_0040809 was highly expressed in CRC cells and tissues; hsa_circ_0040809 upregulates DNMT1 expression by competitively combining with miR-515-5p, thus suppressing apoptosis and promoting cancer progression [115]. Conversely, as a tumor suppressor, circTADA2A was found to be down-regulated in cancer cells and tissues. Overexpression of circTADA2A elevated the expression of KLF14 by targeting miR-374a-3p, thereby promoting cell apoptosis and inhibiting tumor growth [116]. Moreover, has_circ_0001666 is a circRNA originating from exons 2, 3, and 4 of the host gene FAM120B. Studies have demonstrated that hsa_circ_0001666 competitively bound to miR-576-5p to increase PCDH10 expression, which in turn restrained cell stemness and EMT and Wnt/β-catenin pathway [117]. Zhang *et al* [118] revealed that the knockdown of circRNA_103948 contributed to enhanced autophagy of CRC cells by targeting the miR-1236-3p/TPT1 signaling pathway, inhibiting tumor growth. In addition, hypoxia facilitated circCCDC66 expression, which boosted the development of CRC by modulating the miR-3140/autophagy axis [119]. Furthermore, studies observed that hsa_circ_101555 was more highly expressed in CRC tissues than in normal tissues and was associated with adverse prognosis of patients. Inhibition of circ101555 resulted in the initiation of cell apoptosis and devastated DNA repair by activating the miR-597-5p/CDK6/RPA3 axis, thereby repressing the progression of CRC [120]. These studies suggested that circRNAs might be closely associated with the process leading to CRC oxaliplatin resistance.

CircRNAs regulate CRC oxaliplatin resistance

The majority of circRNAs containing miRNA response elements (MREs) can regulate gene expression and signaling pathways by functioning as ceRNAs, mediating tumor chemoresistance [121] (Table 3). Studies have identified that circPTK2 (Circular RNA protein tyrosine kinase 2) was significantly up-regulated in CRC tissues compared to normal tissues, and its high levels of expression promoted CRC progression and oxaliplatin resistance by regulation of the miR-136-5p/ YTHDF1 axis [122]. Similarly, circ_0032833 was highly expressed in FOLFOX-resistant CRC cells, and knock-down of circ_0032833 could promote apoptosis and partially enhance the sensitivity of CRC cells

to 5-FU and oxaliplatin through the activity of miR-125-5p/MSI1 [123]. Lai et al [124] also demonstrated that hsa_circ_0079662 functioned as a "sponge" for hsa-mir-324-5p and activated HOXA9 through the activation of the TNF-α pathway; this process induced oxaliplatin-resistance in CRC cells. Furthermore, our previous research revealed that circHIPK3 was highly expressed in chemoresistance CRC patients, and this circRNA was strongly associated with tumor size, regional lymph node metastasis, and distant metastasis. The following functional investigation revealed that circHIPK3 facilitated oxaliplatin resistance, but not 5-FU resistance, by restraining autophagy-related cell death. Mechanistically, circHIPK3 acted as a ceRNA and a "sponge" for miR-637 resulting in activation of the STAT3/Bcl-2/Beclin1 pathway, and subsequent induction oxaliplatin-resistance in CRC cells [125].

Intriguingly, oxaliplatin could directly induce the overexpression of some oncogenes, further exacerbating chemoresistance. Circular CCDC66, derived from exons 6 to 11, was highly expressed in oxaliplatin-resistant CRC tissues and cells, a phenomenon caused by oxaliplatin-triggered cell stress through phosphoinositide 3-kinase related kinases (PI3KKs)-mediated phosphorylation of DHX9 [126]. Despite extensive literature, many circRNAs remain to be explored in the study of oxaliplatin-resistant CRC. Nadiah et al [127] identified differential expression of circular RNAs when analyzing chemosensitive and chemoresistant CRC cells using microarray; hsa_circ_32883 and hsa_circ_0338 were screened as promising candidates. Subsequently, their study also identified that exosome-derived circRNAs (hsa_circ_0032883, hsa_circ_0002039, and hsa_circ_0000338) may play important roles in the manifestation of chemoresistance [128].

Studies have reported that the expression of exosomal miR-21-5p from oxaliplatin-resistant cells was significantly elevated, and therefore levels of this miRNA could act as a predictor of chemotherapy response in CRC patients [129]. Interestingly, miR-21-5p can be sponged by some tumor-suppressive circRNAs, such as circDDX17 [35] and circEPB41L2 [130], thus resulting in the activation of the downstream PTEN/AKT pathway. Importantly, previous studies have confirmed that targeting the

PTEN/PI3K/AKT/mTOR pathway partially reversed oxaliplatin resistance in CRC [51, 52]. Given this, we speculate that targeting these suppressive circRNAs might contribute to the sensitization of CRC cells to oxaliplatin *via* the miR-21-5p/PTEN/AKT axis. Furthermore, hsa_circ_0001955 and hsa_circ_0000977, potential upstream targets for chemoresistance-associated miRNAs [49, 93], were detected to be dysfunctional in CRC tissue, a finding that suggests these circRNAs may be involved in the progression of CRC chemoresistance in a ceRNA-dependent manner [131]. Currently, studies regarding the roles of circRNAs in oxaliplatin resistance are less commonly reported, the precise and comprehensive mechanisms of circRNAs in CRC chemoresistance need to be explored by further study.

INTEGRATION, APPLICATION, AND CHALLENGES OF TARGETING EXOSOMAL NCRNAS IN CRC CHEMORESISTANCE

Exosomes biogenesis and characterization

Extracellular vesicles (EVs) are defined as a class of membranous vesicles that are released by cells to the extracellular matrix and play a key role in various physiological and pathological processes. According to the difference in their origin, size, content, and biological function, EVs can be roughly divided into three main subtypes—microbubbles, exosomes, and apoptotic bodies [132]. Exosomes are an emerging hallmark of liquid biopsy and have attracted much scientific attention of late, these small disc-shaped EVs have a diameter of approximately 40–150 nm and are enclosed by a lipid bilayer membrane [133]. Almost all cell types can secrete exosomes, and they also exist broadly within fluids including blood, urine, saliva, milk, ascites, cerebrospinal fluid, and others [40, 134]. At present, ultracentrifugation remains the standard method for exosome extraction. However, with the emergence of novel technologies, exosome isolation and purification strategies are being continuously optimized, such as size exclusion chromatography, magnetic bead immune capture, and microfluidic-based chip technology techniques [135], these are aimed at efficiently obtaining exosomes with high abundance and quality. The characterization of exosomes has emerged as a

prerequisite for their utilization, and the three basic characterization modes of morphological identification are particle size distribution and protein markers. However, more advanced features are gradually being included, in exosome characterization, such as the identification of the purity of exosomes and their uptake [135, 136]. As signaling entities, numerous studies have demonstrated that exosomes exert biological effects in two ways: Firstly, exosomal membrane proteins or lipids act as ligands, directly activating receptors at the surface of target cells, generating cascade signal events and activating intracellular signaling pathways; Secondly, exosomes entrain and transport cellular signal-regulating molecules to target cells; these include DNA, lipids, proteins, and RNAs, which are extensively involved in tumorigenesis, metastasis, recurrence, and chemoresistance of cancers [137, 138]. In particular, exosomal ncRNAs have received unprecedented appreciation in biomedical research and clinical application recently [139, 140]. Several exosomal ncRNAs involved in CRC oxaliplatin resistance are listed in Table 4.

The latent mechanisms of exosomal ncRNAs in CRC oxaliplatin resistance

Increasing numbers of reports have revealed that exosomal ncRNAs can mediate chemoresistance *via* remodeling of the tumor microenvironment. Studies have identified that lncRNA H19 is highly expressed in CRC tissues compared to normal tissues. Moreover, lncRNA H19 derived from CAFs can act as a direct "sponge" for miR-141 and activate the β-catenin pathway, thus promoting stemness and oxaliplatin resistance [141]. Likewise, exosomal miR-92a-3p was transmitted from CAFs to cancer cells, promoting chemoresistance *via* the Wnt/β-catenin/apoptosis pathway [20]. Moreover, CAF-derived exosomes were revealed to deliver colorectal cancer-associated lncRNA-associated lncRNA (CCAL) to cancer cells, interacting with the mRNA of stable protein human antigen R (HuR) and increasing the expression of β-catenin; these processes promoted oxaliplatin resistance in CRC cells [142]. Qu *et al* [143] also found that exosomal cricN4BP2L2 secreted by CAFs can interact with EIF4A3 and modulate PI3K/AKT/mTOR signaling pathway, thus promoting oxaliplatin resistance and the stemness of CRC cells. In addition, exosomal circ_0094343 derived from human colonic

epithelial cells (NCM460 cells) was identified to be uptaken by CRC cells in which it regulated cell apoptosis and glycolysis *via* the miR-766-5p/TRIM67 pathway, thereby enhancing the chemosensitivity of tumor cells [144].

Conversely, tumor cells have been revealed to generate exosomes in an autocrine or paracrine manner; they are uptaken by themselves or delivered to the local microenvironment, thus exerting functional regulation. Ning *et al* [145] demonstrated that CRC cell-derived exosomal miR-208b could promote Treg expansion by directly inhibiting the expression of programmed cell death factor 4 (PDCD4), resulting in promoted tumor progression and oxaliplatin resistance. Similarly, studies have revealed that exosomal miR-46146 conferred chemoresistance *via* the targeting of programmed cell death factor 10 (PDCD10) in CRC cells [146]. Interestingly, one particular study revealed that miR-1915-3p was down-regulated in oxaliplatin-resistant CRC cells compared to in sensitive cells and that EVs-derived miR-1915-3p increased the oxaliplatin sensitivity of drug-resistant cells by targeting PFKFB3/USP2 [147]. Moreover, it has been reported that hsa_circ_0005963 (ciRS-122) can be transferred from oxaliplatin-resistant cells to sensitive cells by exosomes, directly acting as a miR-122 "sponge" and increasing the expression of PKM2, which promotes glycolysis and oxaliplatin-resistance in sensitive cells [148].

Exosomal ncRNAs as potential Liquid biopsy biomarkers

Liquid biopsy, in which diseases are evaluated diseases *via* sampling biological fluids, can avoid the influence of tissue heterogeneity on tumor molecular typing to some extent. More and more evidence shows that abundant exosomes are enriched in body fluids and participate in many physiological and pathological processes. As an emerging hallmark of liquid biopsy, exosomes are of substantial value for cancer diagnosis, monitoring, and prediction [136, 140]. Studies found that the ratio of exosomal miRNAs is an effective predictor of tumor response for peritoneal metastatic patients after repeated intraperitoneal (IP) chemotherapy, patients with high ratios of miR-223-3p/miR-29b-3p or miR-21-5p/miR-29b-3p had inferior survival outcomes compared to patients with low ratios [149]. By analogy, exosomes derived miR-21-5p, miR-1246, miR-

1229-5p, and miR-96-5p were highly expressed in CRC patients and cancer cell lines resistant to 5-FU and oxaliplatin compared with those sensitive to chemotherapy. The AUC of four combinations of exosomal miRNAs is 0.804, which is expected to be an effective predictor of chemotherapy [129]. Besides, researchers found that plasma-derived exosomal miRNA-125b was highly expressed in patients with progressive disease (PD) compared with the healthy control group or patients with stable disease (SD). Importantly, some patients with PD who respond to modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) have obvious differences in the expression of plasma exosomal miRNA-125b before and after chemotherapy, and patients with low expression of exosomal miRNA-125b have higher progression-free survival (PFS) [150]. Furthermore, it was reported that miR-208b was highly expressed in the serum of FOLFOX-resistant CRC patients and the area under curve (AUC) of serum miRNA-208b is 0.771 (95% confidence interval [CI], [0.688, 0.855]), which is better than that of serum CEA of 0.493 (95% [CI], [0.385, 0.601]) . Their research suggests that this miRNA can be regarded as a promising liquid biopsy indicator to predict FOLFOX sensitivity in cancer patients [145]. Encouragingly, a panel of plasma exosomal miR-17-5p and miR-185-5p were successfully used to predict FOLFOX4/FOLFIRI responses in patients with advanced CRC [151].

Exosomal ncRNAs as delivery vehicles for chemosensitization

A large number of reports have revealed the prospects for the application of exosomes to overcome chemoresistance, their strong stability, intrinsic biocompatibility, low immunogenicity, and natural targeting ability making them favorable targets [152, 153]. Novel research has exhibited an engineered exosome encapsulating oxaliplatin and PGM5 Antisense RNA 1 (PGM5-AS1) that were delivered into CRC cells, these effectively relieved chemoresistance and inhibited tumor progression [154]. Furthermore, Pi *et al* [155] constructed engineered EVs enwrapped in folate nanoparticles and survivin siRNA, which significantly inhibited tumor growth in CRC xenograft mice. Similarly, miR-21 inhibitors have been co-incorporated into exosomes, resulting in enhanced

chemosensitivity of CRC cells [156]. Taken together, these findings suggest that exogenous delivery of ncRNAs could serve as a novel therapeutic target for CRC.

CONCLUSION

A multitude of emerging studies have confirmed that dysfunctional ncRNAs contribute to the development of malignancies, including chemoresistance. In this review, we systematically summarized the multiple mechanisms by which ncRNAs function in CRC oxaliplatin resistance and discussed the biomedical prospects of exosomal ncRNAs as hallmarks for fluid biopsy and therapeutic targets. Figure 2 schematically illustrates the multiple regulatory roles of ncRNAs in CRC oxaliplatin resistance. Owing to the differential expression patterns of ncRNAs in cancer patients, it is considered they may be used as biomarkers for early detection, tumor staging, and clinical outcome. Although many mechanisms by which ncRNAs exert their biological effects remain to be deciphered, targeting these ncRNAs has emerged as a promising strategy to ameliorate chemoresistance.

Nevertheless, the integration and application of ncRNAs in clinical practice are far from the existing research fervor and are currently being tested in experimental studies; there are still many challenges to be overcome before ncRNAs can be extensively implemented in clinics. Firstly, the results of existing research are confounding due to differing nomenclature being utilized for circRNAs. The circRNAs labeled using different naming standards make the subsequent genomic localization cumbersome. Secondly, the expression of ncRNAs in biological fluids is relatively low, and therefore accurate detection and quantification of these molecules is a prerequisite for the development of biomarkers. Furthermore, due to differences in the lengths and mechanisms by which ncRNAs function in distinct tumor types, it is a challenge to select appropriate targets for these multitudinous candidates. Exosomes may be a better intermediary for delivering ncRNAs therapies; this could be achieved in an endogenous or exogenous manner. However, it is crucial to increase the loading of ncRNAs delivered by endogenous exosomes and ensure the safety of engineered exosomes with

complex structures. Measurements of the efficacy of exosomal ncRNAs in clinical applications cannot be limited to laboratory data alone. A series of large validation cohorts will be required to obtain reliable predictive models and accurate therapeutic doses. In the future, clinical translational trials utilizing target ncRNAs are expected to overcome oxaliplatin resistance and thus improve the clinical outcomes of CRC patients.

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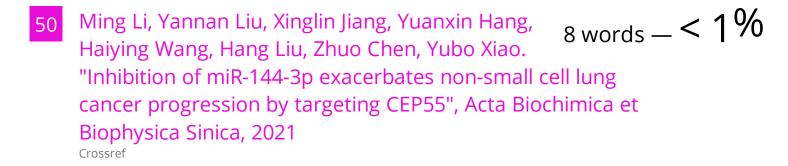Crossref

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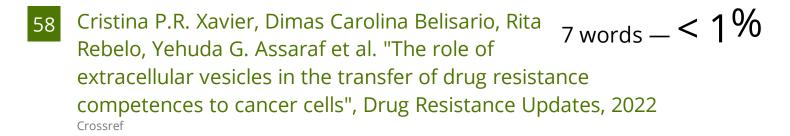Crossref
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