Send Orders for Reprints to reprints@benthamscience.net

Current Cancer Drug Targets, XXXX, *XX*, 1-14

REVIEW ARTICLE

Exploring the Role of Long Non-Coding RNAs in Mediating Cisplatin Resistance in Colorectal Cancer

Shirin Azizidoost[1,#], Omid Anbiyaee[2,#], Atefeh Bahmani[3], Maryam Khombi Shooshtari[4], Pezhman Alavinejad[5], Sara Zarasvandnia[6] and Maryam Farzaneh[7,8,*]

[1]Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [2]Cardiovascular Research Center, Namazi Hospital, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [3]Department of Biology, Faculty of Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran; [4]Chronic Renal Failure Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [5]Alimentary Tract Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [6]Department of Internal Medicine, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [7]Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; [8]Clinical Research Development Unit, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ARTICLEHISTORY

Received: December 06, 2024
Revised: February 05, 2024
Accepted: February 12, 2024

DOI:
10.2174/0115680096376480250408070103

Abstract: Colorectal cancer (CRC) usually begins as adenomatous polyps in the colorectal or rectal epithelial cells. Currently, there are no reliable biomarkers for early CRC screening or prognostic prediction, leading to late-stage diagnoses when surgical options may no longer be viable. The disease is driven by mutations in oncogenes, tumor suppressor genes, and DNA repair genes, with rapid growth and metastasis contributing to treatment failure. Over the past two decades, research on non-coding RNAs (ncRNAs), particularly long ncRNAs (lncRNAs), has expanded significantly, revealing their critical roles in cancer biology. LncRNAs are involved in numerous biological processes such as cell proliferation, apoptosis, metabolism, and drug resistance, and they are often abnormally expressed in various cancers, including hepatocellular carcinoma, pancreatic cancer, and bladder cancer. In CRC, lncRNAs play a regulatory role by influencing cell cycle, proliferation, apoptosis, and epithelial-mesenchymal transition, and some have been shown to affect CRC cell proliferation, invasion, and resistance to cisplatin, highlighting their potential as therapeutic targets and biomarkers in cancer treatment. This review highlights current investigations on the functions and mechanisms of lncRNAs in cisplatin resistance in CRC. Such overview is anticipated to contribute to figuring out that lncRNAs can be applied as a promising target gene to develop drug resistance and remedial efficacy.

Keywords: LncRNAs, colorectal cancer, cisplatin, biomarkers, miRNA, metastasis.

1. INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer and the fourth most common cause of cancer-related death [1]. This type of cancer affects the large intestine (colon) or rectum and is often only diagnosed at an advanced stage, which limits treatment options [2]. Broken down by gender, CRC is the second most common cancer in women (9.2%) and the third most common in men (10%) [3, 4]. This type of cancer originates from an adenomatous polyp in the colorectal or rectal epithelial cells, which results from adenomatous polyposis coli (APC) mutations, a tumor suppressor gene [5]. Not all polyps develop malignant characteristics; those that undergo further changes in other tumor suppressor genes and oncogenes have the potential to progress to adenocarcinoma. This transformation can take several years or even decades to occur. CRC can be classified into three categories: CRC inflammatory, hereditary, and sporadic. Each category arises from changes in the molecular mechanisms that contribute to cancer progression [6]. As there are no early screening and prognostic prediction biomarkers, diagnosis of many subjects only occurs at an advanced stage when surgical treatment is no longer an option [7]. The likelihood of developing CRC is related to personal characteristics or habits such as age, chronic diseases, and lifestyle. CRC is caused by mutations affecting oncogenes, tumor suppressor genes, and genes related to DNA repair mechanisms. Rapid growth, distant metastasis, and drug resistance are the main reasons for treatment failure in CRC [8]. Current treatment approaches for CRC include surgery, chemotherapy, and radiotherapy. The primary purpose of

*Address correspondence to this author at the Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; E-mail: maryamfarzaneh2013@yahoo.com

chemotherapy is to interfere with cell metabolism, DNA replication, mitosis, and protein synthesis of cancer cells to prevent their growth [9]. One of the most common hurdles in the treatment of CRC is undoubtedly chemoresistance progression, which finally results in the failure of chemotherapy, metastatic potential, tumor recurrence, and, unluckily, patient mortality. Multiple chemotherapeutic agents have been approved to inhibit tumor growth, with the most important for colorectal cancer (CRC) being 5-fluorouracil (5-FU), oxaliplatin (OXA), capecitabine, and irinotecan, along with its analogs. [10]. Nonetheless, other drugs, including doxorubicin (DOX) along with cisplatin, have also been considered for the treatment of CRC. Although these various chemotherapeutic agents are efficient, chemoresistance has been exhibited to progress with any of these drugs [11]. Despite advancements in diagnosis and treatment-especially with the introduction of molecularly targeted therapies and immune checkpoint suppressors, the overall prognosis for patients with advanced cancer remains bleak, even as their survival rates have improved. Therefore, it is essential to recognize further new diagnosis biomarkers and targets for cancer treatment.

Over the last two decades, more studies have been published on cellular functions of non-coding RNAs (ncRNAs). Research has demonstrated that the functional disruption of non-coding RNA (ncRNA)-through mutations, transcriptional changes, and post-translational modifications-intends to induce cancer progression [12]. Long non-coding RNAs (lncRNAs), defined as ncRNA transcripts of more than 200 nucleotides, are involved in human diseases' physiological and pathological processes, including cancer [13]. They are associated with many biological processes, including cell proliferation, apoptosis, metabolism, and drug resistance [14]. This type of RNA is abnormally expressed in various tumors, including hepatocellular carcinoma [15], pancreatic cancer [16], and bladder cancer [17]. LncRNAs play an important regulatory role in the development of CRC. Consequently, some studies have indicated that certain factors can influence cellular processes, such as the cell cycle, proliferative capacity, apoptotic ability, and epithelial-mesenchymal transition in colorectal cancer cells. Additionally, some factors have been found to repress the invasion along with the metastatic potential of these cancer cells [18]. Some studies suggest that some lncRNAs affect CRC cell proliferation and invasion and cisplatin resistance [19]. Therefore, understanding the molecular mechanisms and genes involved in cisplatin resistance is pivotal for developing more effective therapeutic strategies against colorectal cancer (CRC). In the current review, we outline novel directions to the essential role of the long non-coding RNAs (lncRNAs) in cisplatin resistance in CRC. Such an overview is anticipated to contribute to figuring out the mechanisms of cisplatin resistance in CRC and the correlation of the expression modulation of multiple lncRNAs.

2. CISPLATIN: BIOGENESIS AND FUNCTION

Cisplatin is recognized as one of the earliest and most effective metal-based chemotherapeutic agents discovered by Michele Peyrone in 1845. However, its biological features stayed largely unknown until 1965, when its cell division inhibitory impact was uncovered by biophysicist Dr. Barnett Rosenberg [20]. It has a complex compound characterized by a planar structure that includes two chlorine atoms and two ammonia molecules arranged in a cis configuration around a platinum atom in its second oxidation state, connected through coordination bonds [21]. This drug is used in various solid malignancies, including testicular, ovarian, bladder, lung, cervical, head and neck, and gastric. Investigations have proved that cisplatin shows its anticancer impact at more than one site. Generally, its binding to genomic or mitochondrial DNA (gDNA or mtDNA) induces DNA lesions, inhibits DNA, mRNA, and protein synthesis, halts DNA replication, and triggers multiple signaling pathways that ultimately lead to apoptosis or necrosis [20]. Cisplatin is administered to patients intravenously in the form of a saline solution. Since it circulates in the bloodstream, the active compound in the drug can readily bind to blood amino acids and proteins such as cysteine and albumin, resulting in 65–95% inactivation of administered cisplatin within the patient's body. The non-inactivated form of cisplatin is taken up by cells through CTR1 and CTR2 as membrane transport proteins, as well as *via* passive diffusion. Once inside the cells, cisplatin becomes activated by replacing one or two chloride ligands with water molecules [21]. It also has a hydrated and activated compound that has multidirectional cytotoxic activity that, among other things, triggers oxidative stress in the cells and damages the cellular and mitochondrial DNA in cancer cells [20, 21]. The main cisplatin cytotoxic target is the genomic DNA. After cell entrance, cisplatin binds to nitrogenous bases in the DNA — with the highest affinity for guanine and adenine at the N7 position of their imidazole rings [20, 22, 23]. Most commonly (65 % of cases), cisplatin binds to two guanines of the same DNA strand or guanine and adenine of the same strand (25 % of cases), resulting in the formation of adducts within the strand. To a lesser extent, in only 5 % of cases, it binds to two guanines located on opposite strands, creating cross-links between the strands [23]. Both intrastrand adducts as well as interstrand cross-links formation results in genetic material damage. The latter is triggered by cisplatin activating mechanisms of DNA repair, basically the nucleotide excision repair (NER) as well as mismatch repair (MMR) ones. If such repair mechanisms fail, apoptosis signalings are triggered within the cell [20, 21]. Such pathway activation can occur, for instance, by suppressing the cell cycle during the G1, S, or G2 phases, resulting in a disruption of DNA synthesis within the cell and ultimately leading to cell death [21, 24].

Mitochondrial DNA (mtDNA) is also considered a target of cisplatin. Similar to its interaction with nuclear DNA, cisplatin binding to mtDNA leads to the formation of adducts and cross-links, resulting in mitochondrial DNA damage [25]. Mitochondrial DNA damage modifies mitochondrial membrane permeability, resulting in cytochrome C as well as procaspase 9 release from the organelle. The binding of mitochondria-released components with APAF-1 and ATP creates an apoptosome, leading to caspase 9 activation. The activated caspase 9 interacts with downstream caspases, activating caspases 3, 6, and 7, which initiate cell apoptosis [20].

Another mechanism of the cytotoxic effect of cisplatin is oxidative stress induction in the cells *via* enhancing the reactive oxygen species production like hydroxyl radicals and

superoxidase. It is believed that there are three key intracellular compartments, including cell membrane, cytoplasm, as well as cellular organelles where cisplatin triggers the ROS formation. In the cell membrane, a significant ROS increase results in acid sphingomyelinase activation, which leads to an accumulation of FAS receptors in the plasma membrane through the hydrolysis of sphingolipids to ceramides, resulting in cell death [26]. Mitochondria are regarded as the most organelles exposed to ROS. Interaction of excess ROS with the pro-apoptotic BAX protein damages and modifies the mitochondrial membrane potential, resulting in apoptosis activation *via* the intrinsic pathway already explained [27]. Nonetheless, cisplatin does not exert its most significant possibility due to complications and drug resistance. Cisplatin resistance relies on several factors, including decreased accumulation of drugs, drug inactivation through various protein binding, increased DNA repair, and modification of various proteins that signal apoptosis [23, 28, 29]. The main toxicities of cisplatin remedy are nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal toxicity, and neurotoxicity [30].

3. THE INTERPLAY BETWEEN LNCRNAS-CISPLATIN IN CRC

The relationship between lncRNAs and cisplatin in CRC is quite intricate, as lncRNAs can either enhance sensitivity to cisplatin or contribute to resistance. This complexity underscores the dual roles that lncRNAs can have, positioning them as promising targets for strategies aimed at boosting the effectiveness of chemotherapy and tackling drug resistance.

4. LINC00461*/MIR-593-5P/CCND1*

The oncogenic function of long intergenic non-protein coding RNA 461 (LINC00461) has been illuminated in human malignancies [31, 32]. High LINC00461 expression has been revealed in colorectal cancer cells [33]. Little investigation has been conducted on the biological effects of miRNA-593-5p in malignancies [34]. It has been shown that LINC00461 loss of function or miR-593-5p overexpression restrained the progression of rectal cancer and increased rectal cancer cell sensitivity to cisplatin. In addition, overexpression of cyclin D1 (CCND1) as a miR-593-5p downstream target could reverse the impact of low expression of LINC00461 on the progression of rectal cancer and rectal cancer resistance to cisplatin [33]. Overall, LINC00461 regulates rectal cancer resistance to cisplatin through targeting the miR-593-5p/CCND1 axis, shedding novel insight into the management of rectal malignancy.

5. KCNQ1OT1/MIR-497/ BCL-2

LncRNA KCNQ1 opposite strand/antisense transcript 1 (KCNQ1OT1) has been shown to be strongly associated with cancer progression [35]**.** It has been shown that KCNQ1OT1 expression was higher in colorectal cancer cell lines that are resistant to cisplatin in comparison to colorectal cancer cell lines. Moreover, functional assay revealed that KCNQ1OT1 deletion repressed proliferative capacity and elevated apoptosis in cisplatin-resistant colorectal cancer cells [36]. *In vitro* assessment revealed the clinical significance of miR-497-low expression in colorectal cancer in a way that its up-regulation restrained colorectal cancer progression [37]. It was found that KCNQ1OT1 could function as a miR-497 sponge, removing the repressive impact of miR-497 on Bcl-2 expression [36]. Over the years, a number of investigations demonstrated the possible impact of curcumin as a natural phenolic compound to fight against cisplatin-resistant cancer cells while the specific mechanism remains unclear [38, 39]. It has been reported that curcumin therapy restrained proliferative activity and facilitated apoptotic potential in cisplatin-resistant colorectal cancer cells. While high expression of KCNQ1OT1 eliminated curcumin impact on such cells through the miR-497/ Bcl-2 axis, thereby highlighting the aggravating role of KCNQ1OT1/miR-497/ Bcl-2 network on cisplatin resistance in colorectal cancer cells [36].

6. LNCRNA PVT1

Deregulated expression of lncRNA PVT1 has been shown to be involved in the pathophysiology of different cancers [40]. Increased PVT1 expression was reported to be positively associated with clinicopathological features of colon cancer and resistance to cisplatin in colorectal cancer patients. Loss of PVT1 function in cisplatin-resistant colorectal cancer cells suppresses proliferation and enhances apoptosis, whereas its high expression promotes proliferative activity and reduces apoptotic potential [8]. A number of evidence exist to defend the assumption that apoptosis failure is regarded as a pivotal cause for drug resistance development [41]. The vital proteins, including Bcl-2, Bax, as well as caspase-3 have key functions in intrinsic apoptosis signaling and are discovered to participate in colorectal cancer multidrug resistance [42]. Additionally, PVT1 has been shown to display colorectal cancer cell anti-apoptotic potential [43]. From a mechanistic standpoint, the levels of drug resistance-correlated molecules such as multidrug resistance protein 1, anti-apoptotic Bcl-2 expression and multidrug resistance 1 were dramatically downregulated whilst pro-apoptotic Bax and cleaved caspase-3 levels were upregulated in PVT1- deleted cisplatin-resistant colorectal cancer cells. In conclusion, it is shown that PVT1 is a notable modulator in carcinogenesis and cisplatin resistance of colorectal cancer, highlighting PVT1 as a promising target for colorectal cancer remedy [8, 44].

7. GALNT5/MDR1/MRP1/NF-KB

GALNT5 uaRNA is known as an lncRNA-derived 3′untranslated region (3′-UTR) of GALNT5 and its deregulation has been reported in various malignancies, including gastric cancer. To elucidate the lncRNA GALNT5 uaRNA function and potential mechanism in cisplatin resistant colorectal cancer, it has been shown that GALNT5 uaRNA is highly expressed in cisplatin-resistant colorectal cancer [45]. Moreover, multiple drug resistance (MDR) is regarded as the most common cause of remedial failure in malignant patients. MDR-correlated proteins such as MDR1, and multidrug resistance proteins (MRPs) are significantly correlated with MDR [46]. Regarding colorectal cancer, MDR1, MRP1 and p-NF-κB expressions and apoptosis were decreased and increased in cisplatin-resistant colorectal cancer cells, re-

spectively. It can be concluded that GALNT5 uaRNA develops cisplatin resistance through the MDR1/MRP1/NF-κB network [45].

8. LINC00261

LINC00261, as a lncRNA, is known to have vital functions in tumor suppression [47]**.** LINC00261 expression has been found to down-regulate in cisplatin-resistant colorectal cancer cells. Indeed, LINC00261 upregulation might mitigate resistance to cisplatin in colorectal cancer cells by inducing cell apoptosis and suppressing cell viability, migratory potential, as well as invasion [48]. Moreover, carcinogenesis is known as a multistep process that is regulated through multiple oncogenic cell pathway cascades, such as the Wnt/b-catenin signal [49]. It has also been reported that LINC00261 might underexpress nuclear b-catenin *via* promoting b-catenin degradation and inhibiting Wnt pathway activation. Ultimately, LINC00261 has been shown to decrease *in vivo* cisplatin resistance of colorectal cancer and induce cisplatin anti-colorectal cancer impact *via* decreasing tumor weight as well as volume, which might propose a novel vision and insight for the management of colorectal cancer [48]. Indeed, miR-324-3p and its correlation with LINC00261 and the Wnt pathway have also been shown to participate in colon cancer progression [50]. *MiR-324-3p* was found to have a correlation with colon cancer. In this regard, overexpression of LINC00261 has been reported to repress colon tumor growth through miR-324-3p sponging and Wnt pathway inactivation. Overall, our results showed that LINC00261 repressed colon cancer progression *via* modulating miR-324-3p and the Wnt signal. LINC00261 could be established as a promising remedial target for colon cancer [50].

9. DANCR/MIR-125B-5P/HK2

The lncRNA differentiation antagonizing non-coding RNA (DANCR) overexpressed in various malignancies, illustrating an oncogenic function of DANCR [51, 52]. Up-regulation of DANCR in cisplatin-resistant colorectal cancer cells has been demonstrated to dramatically desensitize colorectal malignant cells to cisplatin [53]. Emerging data that illuminates the essential roles of miR-125b has reported its possibility as a diagnostic and prognostic marker along with an efficient remedial tool against malignancies [54]. Indeed, DANCR has been reported to have a negative association with miR-125b-5p, whose upregulation notably sensitized cisplatin-resistant colorectal cells. It is of note that colorectal cancer cells that are resistant to cisplatin were correlated with a significantly enhanced glycolysis rate. Deleting endogenous DANCR resulted in dramatic expression of miR-125b-5p and its direct target, hexokinase 2 (HK2), leading to repression of the glycolysis rate and upregulation of sensitivity to cisplatin in colorectal cancer cells. Such a study notified a novel mechanism of the DANCR-induced cisplatin resistance, highlighting the DANCR/miR-125b-5p/HK2 network as a probable target for managing chemoresistant colorectal malignancy [53].

10. TUG1/MIR-195-5P/ HDGF/DDX5/B-CATENIN

LncRNA TUG1 has been found to be pivotal to cancer drug resistance. The oncogenic role of IGF2BP2-stabilized TUG1 has been reported in colorectal cancer [55]. The insulin-like growth factor-2 mRNA-binding protein (IGF2BP) family members has vital effects in tumorigenesis, as well as chemoresistance by influencing ncRNAs' translatability, stability, and localization [56-58]. Emerging evidence has offered that miR-195–5p can modulate neoplastic processes in multiple signals [59]. A deeper mechanical investigation has shown that TUG1 prevented miR-195-5p expression [55]. Hepatoma-derived growth factor (HDGF) is known as a heparin-binding protein that has been deregulated in various malignancies and participated in the regulation of cancer cell behaviors, including apoptotic ability, metastatic capacity, and angiogenesis [60]**.** DEAD-box RNA helicase DDX5 (DDX5) is also shown to be involved in the activation of transcription factors to function in malignant occurrence and development [61]. On the other hand, miR-195-5p has been demonstrated to magnify the HDGF/ DDX/β-catenin network triggering autophagy, thereby stepping up *in vitro and in vivo* growth of colorectal cancer cells and their resistance to cisplatin, hinting TUG1/miR-195-5p/ HDGF/DDX5/β-catenin network as an underlying target for the management of colorectal cancer [55].

CONCLUSION

The interactions between lncRNAs and cisplatin in CRC present a complex landscape that significantly impacts treatment outcomes. As research has demonstrated, specific lncRNAs, such as KCNQ1OT1, LINC00461, PVT1, GALNT5, LINC00261, DANCR, and TUG1, play critical roles in mediating cisplatin resistance by influencing various cellular processes. The upregulation of these lncRNAs in CRC cells correlates with decreased sensitivity to cisplatin, highlighting their oncogenic potential. Understanding the mechanisms by which lncRNAs contribute to cisplatin resistance can lead to novel therapeutic strategies aimed at overcoming this challenge.

Despite several successes in cell-based tests for lncRNA-based remedies, clinical trials are essential for the development of remedial interventions that can benefit patients suffering from CRC, but with increasing understanding and accumulating investigations, the clinical potential of targeting lncRNAs appears highly promising in the near future. Of course, substantial work is required to be done for the lncRNA-based tumor treatment to be used in clinical practice. Chemoresistance is a complex biological process, and the roles and mechanisms of lncRNAs in this process remain poorly understood. Most studies are conducted *in vitro*, while meaningful functional investigations often depend on animal models.. The lncRNA sequence conservation represents much poorer compared to protein-coding genes. As a remedial strategy, the technology for either deletion or up-regulation of a particular lncRNA at a special target gene *in vivo* is still in progression. To develop sensitive and specific biomarkers, it is essential to create clinically applicable diagnostic and prognostic experiments according to the lncRNA markers or marker panels. Additionally, validating their specificity and sensitivity using large sample cohorts is crucial. Importantly, lncRNAs have the ability to modulate multiple targets simultaneously and may participate in complex feedback mechanisms. Therefore, potential off-target effects must be carefully considered in future applications.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Azizidoost, S.; Nasrolahi, A.; Ghaedrahmati, F.; Kempisty, B.; Mozdziak, P.; Radoszkiewicz, K.; Farzaneh, M. The pathogenic roles of lncRNA-Taurine upregulated 1 (TUG1) in colorectal cancer. *Cancer Cell Int.*, **2022**, *22*(1), 335. http://dx.doi.org/10.1186/s12935-022-02745-1 PMID: 36333703

[2] White, M.T.; Sears, C.L. The microbial landscape of colorectal cancer. *Nat. Rev. Microbiol.*, **2024**, *22*(4), 240-254. http://dx.doi.org/10.1038/s41579-023-00973-4 PMID: 37794172

[3] Cherkasova, V.; Ilnytskyy, Y.; Kovalchuk, O.; Kovalchuk, I. Targeting colorectal cancer: Unravelling the transcriptomic impact of cisplatin and high-THC cannabis extract. *Int. J. Mol. Sci.*, **2024**, *25*(8), 4439. http://dx.doi.org/10.3390/ijms25084439 PMID: 38674023

[4] Mármol, I.; Sánchez-de-Diego, C.; Pradilla Dieste, A.; Cerrada, E.; Rodriguez Yoldi, M. Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. *Int. J. Mol. Sci.*, **2017**, *18*(1), 197. http://dx.doi.org/10.3390/ijms18010197 PMID: 28106826

[5] Maida, M.; Dahiya, D.S.; Shah, Y.R.; Tiwari, A.; Gopakumar, H.; Vohra, I.; Khan, A.; Jaber, F.; Ramai, D.; Facciorusso, A. Screening and surveillance of colorectal cancer: A review of the literature. *Cancers*, **2024**, *16*(15), 2746. http://dx.doi.org/10.3390/cancers16152746 PMID: 39123473

[6] Nguyen, H.; Duong, H.Q. The molecular characteristics of colorectal cancer: Implications for diagnosis and therapy (Review). *Oncol. Lett.*, **2018**, *16*(1), 9-18. http://dx.doi.org/10.3892/ol.2018.8679 PMID: 29928381

[7] Benitez-Majano, S.; Fowler, H.; Maringe, C.; Di Girolamo, C.; Rachet, B. Deriving stage at diagnosis from multiple population-based sources: Colorectal and lung cancer in England. *Br. J. Cancer*, **2016**, *115*(3), 391-400. http://dx.doi.org/10.1038/bjc.2016.177 PMID: 27328310

[8] Ping, G.; Xiong, W.; Zhang, L.; Li, Y.; Zhang, Y.; Zhao, Y. Silencing long noncoding RNA PVT1 inhibits tumorigenesis and cisplatin resistance of colorectal cancer. *Am. J. Transl. Res.*, **2018**, *10*(1), 138-149. PMID: 29423000

[9] Pan, J.J.; Xie, X.J.; Li, X.; Chen, W. Long non-coding RNAs and drug resistance. *Asian Pac. J. Cancer Prev.*, **2016**, *16*(18), 8067-8073. http://dx.doi.org/10.7314/APJCP.2015.16.18.8067 PMID: 26745040

[10] Gherman, A.; Balacescu, L.; Gheorghe-Cetean, S.; Vlad, C.; Balacescu, O.; Irimie, A.; Lisencu, C. Current and new predictors for treatment response in metastatic colorectal cancer. The role of circulating miRNAs as biomarkers. *Int. J. Mol. Sci.*, **2020**, *21*(6), 2089. http://dx.doi.org/10.3390/ijms21062089 PMID: 32197436

[11] Jiang, W.; Yan, Y.; Chen, M.; Luo, G.; Hao, J.; Pan, J.; Hu, S.; Guo, P.; Li, W.; Wang, R.; Zuo, Y.; Sun, Y.; Sui, S.; Yu, W.; Pan, Z.; Zou, K.; Zheng, Z.; Deng, W.; Wu, X.; Guo, W. Aspirin enhances the sensitivity of colon cancer cells to cisplatin by abrogating the binding of NF-κB to the COX-2 promoter. *Aging*, **2020**, *12*(1), 611-627. http://dx.doi.org/10.18632/aging.102644 PMID: 31905343

[12] Micallef, I.; Baron, B. The mechanistic roles of ncRNAs in promoting and supporting chemoresistance of colorectal cancer. *Noncoding RNA*, **2021**, *7*(2), 24. http://dx.doi.org/10.3390/ncrna7020024 PMID: 33807355

[13] Di Martino, M.T.; Riillo, C.; Scionti, F.; Grillone, K.; Polerà, N.; Caracciolo, D.; Arbitrio, M.; Tagliaferri, P.; Tassone, P. miRNAs and lncRNAs as novel therapeutic targets to improve cancer immunotherapy. *Cancers*, **2021**, *13*(7), 1587. http://dx.doi.org/10.3390/cancers13071587 PMID: 33808190

[14] Fu, D.; Lu, C.; Qu, X.; Li, P.; Chen, K.; Shan, L.; Zhu, X. LncRNA TTN-AS1 regulates osteosarcoma cell apoptosis and drug resistance *via* the miR-134-5p/MBTD1 axis. *Aging*, **2019**, *11*(19), 8374-8385. http://dx.doi.org/10.18632/aging.102325 PMID: 31600142

[15] Wei, L.; Wang, X.; Lv, L.; Liu, J.; Xing, H.; Song, Y.; Xie, M.; Lei, T.; Zhang, N.; Yang, M. The emerging role of microRNAs and long noncoding RNAs in drug resistance of hepatocellular carcinoma. *Mol. Cancer*, **2019**, *18*(1), 147. http://dx.doi.org/10.1186/s12943-019-1086-z PMID: 31651347

[16] Xiong, G.; Liu, C.; Yang, G.; Feng, M.; Xu, J.; Zhao, F.; You, L.; Zhou, L.; Zheng, L.; Hu, Y.; Wang, X.; Zhang, T.; Zhao, Y. Long noncoding RNA GSTM3TV2 upregulates LAT2 and OLR1 by competitively sponging let-7 to promote gemcitabine resistance in pancreatic cancer. *J. Hematol. Oncol.*, **2019**, *12*(1), 97. http://dx.doi.org/10.1186/s13045-019-0777-7 PMID: 31514732

[17] Martens-Uzunova, E.S.; Böttcher, R.; Croce, C.M.; Jenster, G.; Visakorpi, T.; Calin, G.A. Long noncoding RNA in prostate, bladder, and kidney cancer. *Eur. Urol.*, **2014**, *65*(6), 1140-1151. http://dx.doi.org/10.1016/j.eururo.2013.12.003 PMID: 24373479

[18] Kaller, M.; Götz, U.; Hermeking, H. Loss of p53-inducible long non-coding RNA *LINC01021* increases chemosensitivity. *Oncotarget*, **2017**, *8*(61), 102783-102800. http://dx.doi.org/10.18632/oncotarget.22245 PMID: 29262524

[19] Zhao, C.; Jiang, Q.; Chen, L.; Chen, W. LncRNA LINC01535 promotes colorectal cancer development and chemoresistance by sponging miR-761. *Exp. Ther. Med.*, **2021**, *22*(1), 685. http://dx.doi.org/10.3892/etm.2021.10117 PMID: 33986850

[20] Ghosh, S. Cisplatin: The first metal based anticancer drug. *Bioorg. Chem.*, **2019**, *88*, 102925. http://dx.doi.org/10.1016/j.bioorg.2019.102925 PMID: 31003078

[21] Zoń, A.; Bednarek, I. Cisplatin in ovarian cancer treatment—known limitations in therapy force new solutions. *Int. J. Mol. Sci.*, **2023**, *24*(8), 7585. http://dx.doi.org/10.3390/ijms24087585 PMID: 37108749

[22] Baik, M.H.; Friesner, R.A.; Lippard, S.J. Theoretical study of cisplatin binding to purine bases: Why does cisplatin prefer guanine over adenine? *J. Am. Chem. Soc.*, **2003**, *125*(46), 14082-14092. http://dx.doi.org/10.1021/ja036960d PMID: 14611245

[23] Rocha, C.R.R.; Silva, M.M.; Quinet, A.; Cabral-Neto, J.B.; Menck, C.F.M. DNA repair pathways and cisplatin resistance: An intimate relationship. *Clinics*, **2018**, *73*(Suppl. 1), e478s. http://dx.doi.org/10.6061/clinics/2018/e478s PMID: 30208165

[24] Chandra, A.; Pius, C.; Nabeel, M.; Nair, M.; Vishwanatha, J.K.; Ahmad, S.; Basha, R. Ovarian cancer: Current status and strategies for improving therapeutic outcomes. *Cancer Med.*, **2019**, *8*(16), 7018-7031. http://dx.doi.org/10.1002/cam4.2560 PMID: 31560828

[25] Borkar, P.; Bhandari, P.; Yadav, S.; Prabhu, A. Cisplatin resistance in ovarian cancer: Classical outlook and newer perspectives. *Biomed. Pharmacol. J.*, **2021**, *14*(4), 1993-2005. http://dx.doi.org/10.13005/bpj/2297

[26] Brozovic, A.; Ambriović-Ristov, A.; Osmak, M. The relationship between cisplatin-induced reactive oxygen species, glutathione, and

BCL-2 and resistance to cisplatin. *Crit. Rev. Toxicol.*, **2010**, *40*(4), 347-359.
http://dx.doi.org/10.3109/10408441003601836 PMID: 20163198

[27] Xu, J.; Gewirtz, D.A. Is autophagy always a barrier to cisplatin therapy? *Biomolecules*, **2022**, *12*(3), 463.
http://dx.doi.org/10.3390/biom12030463 PMID: 35327655

[28] Siddik, Z.H. Cisplatin: Mode of cytotoxic action and molecular basis of resistance. *Oncogene*, **2003**, *22*(47), 7265-7279.
http://dx.doi.org/10.1038/sj.onc.1206933 PMID: 14576837

[29] Skowron, M.A.; Melnikova, M.; Van Roermund, J.G.H.; Romano, A.; Albers, P.; Thomale, J.; Schulz, W.A.; Niegisch, G.; Hoffmann, M.J. Multifaceted mechanisms of cisplatin resistance in long-term treated urothelial carcinoma cell lines. *Int. J. Mol. Sci.*, **2018**, *19*(2), 590.
http://dx.doi.org/10.3390/ijms19020590 PMID: 29462944

[30] Manohar, S.; Leung, N. Cisplatin nephrotoxicity: A review of the literature. *J. Nephrol.*, **2018**, *31*(1), 15-25.
http://dx.doi.org/10.1007/s40620-017-0392-z PMID: 28382507

[31] Ji, D.; Wang, Y.; Li, H.; Sun, B.; Luo, X. Long non-coding RNA LINC00461/miR-149-5p/LRIG2 axis regulates hepatocellular carcinoma progression. *Biochem. Biophys. Res. Commun.*, **2019**, *512*(2), 176-181.
http://dx.doi.org/10.1016/j.bbrc.2019.03.049 PMID: 30879766

[32] Dong, L.; Qian, J.; Chen, F.; Fan, Y.; Long, J. LINC00461 promotes cell migration and invasion in breast cancer through miR-30a-5p/integrin β3 axis. *J. Cell. Biochem.*, **2019**, *120*(4), 4851-4862.
http://dx.doi.org/10.1002/jcb.27435 PMID: 30623482

[33] Qu, W.; Huang, W.; Yang, F.; Ju, H.; Zhu, G. Long noncoding RNA LINC00461 mediates cisplatin resistance of rectal cancer *via* miR-593-5p/CCND1 axis. *Biomed. Pharmacother.*, **2020**, *124*, 109740.
http://dx.doi.org/10.1016/j.biopha.2019.109740 PMID: 31972361

[34] Yan, L.; Zhang, Y.; Li, K.; Wang, M.; Li, J.; Qi, Z.; Wu, J.; Wang, Z.; Ling, L.; Liu, H.; Wu, Y.; Lu, X.; Xu, L.; Zhu, Y.; Zhang, Y. miR-593-5p inhibit cell proliferation by targeting PLK1 in non small cell lung cancer cells. *Pathol. Res. Pract.*, **2020**, *216*(2), 152786.
http://dx.doi.org/10.1016/j.prp.2019.152786 PMID: 31864714

[35] Zhan, K.; Pan, H.; Zhou, Z.; Tang, W.; Ye, Z.; Huang, S.; Luo, L. Biological role of long non-coding RNA KCNQ1OT1 in cancer progression. *Biomed. Pharmacother.*, **2023**, *169*, 115876.
http://dx.doi.org/10.1016/j.biopha.2023.115876 PMID: 37976888

[36] Zheng, Z.; You, H.; Feng, Y.; Zhang, Z. LncRNA KCNQ1OT1 is a key factor in the reversal effect of curcumin on cisplatin resistance in the colorectal cancer cells. *Mol. Cell. Biochem.*, **2021**, *476*(7), 2575-2585.
http://dx.doi.org/10.1007/s11010-020-03856-x PMID: 32757174

[37] Cui, Z.; Han, B.; Wang, X.; Li, Z.; Wang, J.; Lv, Y. Long non-coding RNA TTN-AS1 promotes the proliferation and invasion of colorectal cancer cells by activating miR-497-mediated PI3K/Akt/mTOR signaling. *OncoTargets Ther.*, **2019**, *12*, 11531-11539.
http://dx.doi.org/10.2147/OTT.S229104 PMID: 31920341

[38] Zendehdel, E.; Abdollahi, E.; Momtazi-Borojeni, A.A.; Korani, M.; Alavizadeh, S.H.; Sahebkar, A. The molecular mechanisms of curcumin's inhibitory effects on cancer stem cells. *J. Cell. Biochem.*, **2019**, *120*(4), 4739-4747.
http://dx.doi.org/10.1002/jcb.27757 PMID: 30269360

[39] Rezaee, R.; Momtazi, A.A.; Monemi, A.; Sahebkar, A. Curcumin: A potentially powerful tool to reverse cisplatin-induced toxicity. *Pharmacol. Res.*, **2017**, *117*, 218-227.
http://dx.doi.org/10.1016/j.phrs.2016.12.037 PMID: 28042086

[40] Wu, F.; Zhu, Y.; Zhou, C.; Gui, W.; Li, H.; Lin, X. Regulation mechanism and pathogenic role of lncRNA plasmacytoma variant translocation 1 (*PVT1*) in human diseases. *Genes Dis.*, **2023**, *10*(3), 901-914.
http://dx.doi.org/10.1016/j.gendis.2022.05.037 PMID: 37396533

[41] Neophytou, C.M.; Trougakos, I.P.; Erin, N.; Papageorgis, P. Apoptosis deregulation and the development of cancer multi-drug resistance. *Cancers*, **2021**, *13*(17), 4363.
http://dx.doi.org/10.3390/cancers13174363 PMID: 34503172

[42] Lin, G.L.; Ting, H.J.; Tseng, T.C.; Juang, V.; Lo, Y.L. Modulation of the mRNA-binding protein HuR as a novel reversal mechanism of epirubicin-triggered multidrug resistance in colorectal cancer cells. *PLoS One*, **2017**, *12*(10), e0185625.
http://dx.doi.org/10.1371/journal.pone.0185625 PMID: 28968471

[43] Takahashi, Y.; Sawada, G.; Kurashige, J.; Uchi, R.; Matsumura, T.; Ueo, H.; Takano, Y.; Eguchi, H.; Sudo, T.; Sugimachi, K.; Yamamoto, H.; Doki, Y.; Mori, M.; Mimori, K. Amplification of PVT-1 is involved in poor prognosis *via* apoptosis inhibition in colorectal cancers. *Br. J. Cancer*, **2014**, *110*(1), 164-171.
http://dx.doi.org/10.1038/bjc.2013.698 PMID: 24196785

[44] Guo, H.; Zhao, L.; Shi, B.; Bao, J.; Zheng, D.; Zhou, B.; Shi, J. GALNT5 uaRNA promotes gastric cancer progression through its interaction with HSP90. *Oncogene*, **2018**, *37*(33), 4505-4517.
http://dx.doi.org/10.1038/s41388-018-0266-4 PMID: 29743591

[45] Zhong, Z.; Bai, R.; Xu, J. LncRNA GALNT5 uaRNA promotes cisplatin resistance in colorectal cancer *via* NF-κB/MDR1/MRP1/pathway. *Research Square*, **2022**.
http://dx.doi.org/10.21203/rs.3.rs-1624750/v1

[46] Kadkol, H.; Jain, V.; Patil, A. Multi drug resistance in cancer therapy-an overview. *J. Crit. Rev.*, **2019**, *6*(6), 1-6.
http://dx.doi.org/10.22159/jcr.2019v6i6.35673

[47] Wang, Y.; Xue, K.; Guan, Y.; Jin, Y.; Liu, S.; Wang, Y.; Liu, S.; Wang, L.; Han, L. Long noncoding RNA LINC00261 suppresses cell proliferation and invasion and promotes cell apoptosis in human choriocarcinoma. *Oncol. Res.*, **2017**, *25*(5), 733-742.
http://dx.doi.org/10.3727/096504016X14772362173376 PMID: 27983929

[48] Wang, Z.K.; Yang, L.; Wu, L.L.; Mao, H.; Zhou, Y.H.; Zhang, P.F.; Dai, G.H. Long non-coding RNA LINC00261 sensitizes human colon cancer cells to cisplatin therapy. *Braz. J. Med. Biol. Res.*, **2018**, *51*(2), e6793.
http://dx.doi.org/10.1590/1414-431x20176793 PMID: 29267503

[49] Rahmani, F.; Tadayyon Tabrizi, A.; Hashemian, P.; Alijannejad, S.; Rahdar, H.A.; Ferns, G.A.; Hassanian, S.M.; Shahidsales, S.; Avan, A. Role of regulatory miRNAs of the Wnt/ β-catenin signaling pathway in tumorigenesis of breast cancer. *Gene*, **2020**, *754*, 144892.
http://dx.doi.org/10.1016/j.gene.2020.144892 PMID: 32534060

[50] Yan, D.; Liu, W.; Liu, Y.; Luo, M. LINC00261 suppresses human colon cancer progression *via* sponging miR-324-3p and inactivating the Wnt/β-catenin pathway. *J. Cell. Physiol.*, **2019**, *234*(12), 22648-22656.
http://dx.doi.org/10.1002/jcp.28831 PMID: 31183860

[51] Wang, Y.; Lu, Z.; Wang, N.; Feng, J.; Zhang, J.; Luan, L.; Zhao, W.; Zeng, X. Long noncoding RNA DANCR promotes colorectal cancer proliferation and metastasis *via* miR-577 sponging. *Exp. Mol. Med.*, **2018**, *50*(5), 1-17.
http://dx.doi.org/10.1038/s12276-018-0082-5 PMID: 29717105

[52] Yuan, S.; Wang, J.; Yang, F.; Tao, Q.; Zhang, J.; Wang, L.; Yang, Y.; Liu, H.; Wang, Z.; Xu, Q.; Fan, J.; Liu, L.; Sun, S.; Zhou, W. Long noncoding RNA DANCR increases stemness features of hepatocellular carcinoma by derepression of CTNNB1. *Hepatology*, **2016**, *63*(2), 499-511.
http://dx.doi.org/10.1002/hep.27893 PMID: 25964079

[53] Shi, H.; Li, K.; Feng, J.; Liu, G.; Feng, Y.; Zhang, X. LncRNA-DANCR interferes with miR-125b-5p/HK2 axis to desensitize colon cancer cells to cisplatin vis activating anaerobic glycolysis. *Front. Oncol.*, **2020**, *10*, 1034.
http://dx.doi.org/10.3389/fonc.2020.01034 PMID: 32766131

[54] Peng, B.; Theng, P.Y.; Le, M.T.N. Essential functions of miR-125b in cancer. *Cell Prolif.*, **2021**, *54*(2), e12913.
http://dx.doi.org/10.1111/cpr.12913 PMID: 33332677

[55] Xia, C.; Li, Q.; Cheng, X.; Wu, T.; Gao, P.; Gu, Y. Insulin-like growth factor 2 mRNA-binding protein 2-stabilized long non-coding RNA Taurine up-regulated gene 1 (TUG1) promotes cisplatin-resistance of colorectal cancer *via* modulating autophagy. *Bioengineered*, **2022**, *13*(2), 2450-2469.
http://dx.doi.org/10.1080/21655979.2021.2012918 PMID: 35014946

[56] Huang, X.; Zhang, H.; Guo, X.; Zhu, Z.; Cai, H.; Kong, X. Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in cancer. *J. Hematol. Oncol.*, **2018**, *11*(1), 88.
http://dx.doi.org/10.1186/s13045-018-0628-y PMID: 29954406

[57] Fakhraldeen, S.A.; Clark, R.J.; Roopra, A.; Chin, E.N.; Huang, W.; Castorino, J.; Wisinski, K.B.; Kim, T.; Spiegelman, V.S.; Alexan-

der, C.M. Two isoforms of the RNA binding protein, coding region determinant-binding protein (CRD-BP/IGF2BP1), are expressed in breast epithelium and support clonogenic growth of breast tumor cells. *J. Biol. Chem.*, **2015**, *290*(21), 13386-13400. http://dx.doi.org/10.1074/jbc.M115.655175 PMID: 25861986

[58] Zhi, S.; Li, J.; Kong, X.; Xie, X.; Zhang, Q.; Fang, G. Insulin-like growth factor 2 mRNA binding protein 2 regulates proliferation, migration, and angiogenesis of keratinocytes by modulating heparanase stability. *Bioengineered*, **2021**, *12*(2), 11267-11276. http://dx.doi.org/10.1080/21655979.2021.2002495 PMID: 34753397

[59] Xu, Q.; Xu, J.L.; Chen, W.Q.; Xu, W.X.; Song, Y.X.; Tang, W.J.; Xu, D.; Jiang, M.P.; Tang, J. Roles and mechanisms of miR-195–5p in human solid cancers. *Biomed. Pharmacother.*, **2022**, *150*, 112885. http://dx.doi.org/10.1016/j.biopha.2022.112885 PMID: 35453003

[60] Bao, C.; Wang, J.; Ma, W.; Wang, X.; Cheng, Y. HDGF: A novel jack-of-all-trades in cancer. *Future Oncol.*, **2014**, *10*(16), 2675-2685. http://dx.doi.org/10.2217/fon.14.194 PMID: 25236340

[61] Nyamao, R.M.; Wu, J.; Yu, L.; Xiao, X.; Zhang, F.M. Roles of DDX5 in the tumorigenesis, proliferation, differentiation, metastasis and pathway regulation of human malignancies. *Biochim. Biophys. Acta Rev. Cancer*, **2019**, *1871*(1), 85-98. http://dx.doi.org/10.1016/j.bbcan.2018.11.003 PMID: 30419318