

Non-coding RNAs in drug and radiation resistance of bone and soft-tissue sarcoma: a systematic review

Huan-Huan Chen¹, Tie-Ning Zhang², Fang-Yuan Zhang^{3*}, Tao Zhang^{2*}

¹Department of Oncology, Shengjing Hospital of China Medical University, Shenyang, China; ²Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, China; ³Department of General Surgery, Shengjing Hospital of China Medical University, Shenyang, China

Abstract

Background: Sarcomas comprise approximately 1% of all human malignancies; treatment resistance is one of the major reasons for the poor prognosis of sarcomas. Accumulating evidence suggests that non-coding RNAs (ncRNAs), including miRNAs, long ncRNAs, and circular RNAs, are important molecules involved in the crosstalk between resistance to chemotherapy, targeted therapy, and radiotherapy via various pathways.

Methods: We searched the PubMed (MEDLINE) database for articles regarding sarcoma-associated ncRNAs from inception to August 17, 2022. Studies investigating the roles of host-derived miRNAs, long ncRNAs, and circular RNAs in sarcoma were included. Data relating to the roles of ncRNAs in therapeutic regulation and their applicability as biomarkers for predicting the therapeutic response of sarcomas were extracted. Two independent researchers assessed the quality of the studies using the Würzburg Methodological Quality Score (W-MeQS).

Results: Observational studies revealed the ectopic expression of ncRNAs in sarcoma patients who had different responses to antitumor treatments. Experimental studies have confirmed crosstalk between cellular pathways pertinent to chemotherapy, targeted therapy, and radiotherapy resistance. Of the included studies, W-MeQS scores ranged from 3 to 10 (average score = 5.42). Of the 12 articles that investigated ncRNAs as biomarkers, none included a validation cohort. Selective reporting of the sensitivity, specificity, and receiver operating curves was common.

Conclusions: Although ncRNAs appear to be good candidates as biomarkers for predicting treatment response and therapeutics for sarcoma, their differential expression across tissues complicates their application. Further research regarding their potential for inhibiting or activating these regulatory molecules to reverse treatment resistance may be useful.

Funding: This study's literature retrieval was supported financially by the 345 Talent Project of Shengjing Hospital of China Medical University (M0949 to Tao Zhang).

***For correspondence:**

fyzhang@cmu.edu.cn (F-YuanZ);
zhangtaocmu7@126.com (TZ)

Competing interest: The authors declare that no competing interests exist.

Funding: See page 14

Preprinted: 07 April 2022

Received: 21 April 2022

Accepted: 02 November 2022

Published: 03 November 2022

Reviewing Editor: Renata Pasqualini, Rutgers University, United States

© Copyright Chen et al. This article is distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use and redistribution provided that the original author and source are credited.

Editor's evaluation

Sarcomas comprise approximately 1% of all human malignancies; treatment resistance is one of the major reasons for the poor prognosis of sarcomas. The authors searched the PubMed (MEDLINE) database for articles regarding sarcoma-associated non-coding RNAs from inception to August 17, 2022. Data regarding the roles of ncRNAs in therapeutic regulation and their applicability as biomarkers for predicting the therapeutic response of sarcomas were extracted. The conclusions reached are valuable and solid and should be of interest to the field.

Introduction

Sarcomas constitute a heterogeneous group of rare tumors representing more than 60 malignancies within a wider range of over 160 different bone and soft tissue neoplasms. Sarcomas include bone sarcoma (osteosarcoma [OS], chondrosarcoma, Ewing's sarcoma [EWS]) and soft-tissue sarcomas (Kaposi's sarcoma, rhabdomyosarcoma [RMS], gastrointestinal stromal tumor [GIST]; [Nacev et al., 2020](#)). Epidemiologically sarcomas are uncommon, comprising only approximately 1% of human malignancies ([Siegel et al., 2018](#)), with an estimated annual incidence rate of 2.4 cases per 100,000 population ([Ritter and Bielack, 2010](#); [Wibmer et al., 2010](#)). Treatment strategies include surgical resection, chemotherapy, targeted therapy, immunotherapy, and radiotherapy. Nevertheless, primary or acquired resistance to drugs or radiation eventually leads to treatment failure and poor outcomes in sarcoma patients ([Chen et al., 2016b](#); [Wisdom et al., 2020](#)). The precise mechanisms involved in drug or radiation resistance in sarcoma remain unclear. A better understanding of the mechanisms of sarcoma resistance to drugs or radiation is needed to improve therapeutic efficacy and to prolong the overall survival of patients.

Recently, several lines of evidence have demonstrated that non-coding RNAs (ncRNAs), including miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), play vital roles in the resistance to a variety of therapies against bone and soft-tissue sarcomas, including chemotherapy reagents ([Fu et al., 2019](#)), targeted therapy drugs ([Cao et al., 2016](#)), immune checkpoint inhibitors (ICIs; [Pang and Hao, 2021](#)), and radiation ([He et al., 2020](#)).

miRNAs, which are typically 18–25 nucleotides long, are the most frequently studied short ncRNAs ([Cho, 2010](#)). Mature miRNAs inhibit target gene expression through mRNA degradation or repression of translation ([Vicente et al., 2016](#)). By targeting the repressors of specific genes, miRNAs can be used to upregulate the expression of these genes indirectly by alleviating their repression ([Hulshoff et al., 2019](#)). Increasing evidence has also described a non-canonical role for miRNAs in transcriptional regulation; however, the underlying mechanisms remain largely unknown. ncRNAs comprising over 200 nucleotides are classified as lncRNAs. lncRNAs modulate gene transcription and translation in the cytoplasm through multiple mechanisms ([Chillón and Marcia, 2020](#)). They can act as recruiters, tethers, and scaffolds for other regulatory factors involved in epigenetic modifications or can regulate gene transcription by acting as decoys, coregulators, or polymerase-II inhibitors. They are also involved in the organization of different components of the transcriptional and splicing machinery and the subnuclear structures. Moreover, lncRNAs can control processes such as mRNA processing, stability, and translation by acting as sponges for miRNAs to block their effects ([Kung et al., 2013](#)). Finally, circRNAs comprise 1–5 introns or exons and are highly stable molecules that form a covalently closed continuous loop ([Hentze and Preiss, 2013](#); [Wilusz and Sharp, 2013](#)). Similar to lncRNAs, circRNAs also function as miRNA sponges, RNA-binding protein-sequestering factors, and regulators of gene expression by controlling mRNA transcription ([Li et al., 2015](#); [Hansen et al., 2013](#)). Furthermore, circRNAs can control gene transcription by interacting with phosphorylated polymerase-II or by competing with the pre-mRNA splicing machinery ([Zhang et al., 2013](#); [Ashwal-Fluss et al., 2014](#)).

The primary aim of this systematic review was to discuss new paradigms of the roles of regulatory ncRNAs in the molecular mechanisms that underlie the resistance of sarcomas to treatment. The secondary aim of this review was to identify the applicability of ncRNAs as biomarkers for predicting treatment responses, as well as their potential as therapeutic targets.

Methods

Search strategy

We searched for relevant articles in PubMed using following Medical Subject Headings: ([non-coding RNA] OR [ncRNA] OR [long non-coding RNA] OR [lncRNA] OR [circular RNA] OR [circRNA] OR [miRNA]) AND ([sarcoma] OR [OS] OR [chondrosarcoma] OR [synovial sarcoma] OR [leiomyosarcoma] OR [liposarcoma] OR [fibrosarcoma] OR [Kaposi's sarcoma] OR [RMS] OR [EWS] OR [angiosarcoma] OR [hemangiosarcoma] OR [GIST] OR [epithelioid sarcoma] OR [alveolar soft part sarcoma] OR [clear cell sarcoma] OR [intimal sarcoma] OR [undifferentiated sarcoma] OR [undifferentiated spindle cell sarcoma] OR [undifferentiated pleomorphic sarcoma] OR [undifferentiated round cell sarcoma] OR [epithelioid inflammatory myofibroblastic sarcoma] OR [myxoinflammatory fibroblastic sarcoma] OR [myofibroblastic sarcoma] OR [ectomesenchymoma] OR [malignant solitary fibrous tumor] OR

[malignant tenosynovial giant cell tumor] OR [epithelioid hemangioendothelioma] OR [malignant glomus tumor] OR [malignant peripheral nerve sheath tumor] OR [malignant granular cell tumor] OR [malignant perineurioma] OR [Neurotrophic tyrosine receptor kinase (NTRK)-rearranged spindle cell neoplasm] OR [desmoplastic small round cell tumor] OR [rhabdoid tumor] OR [desmoid tumor] OR [malignant perivascular epithelioid tumor] OR [malignant ossifying fibromyxoid tumor] OR [myoepithelial carcinoma] OR [malignant mixed tumor] OR [hyalinizing spindle cell tumor] OR [malignant Triton tumor] OR [malignant mesenchymoma] AND ([resistance] OR [drug resistance] OR [chemoresistance] OR [chemotherapy resistance] OR [radioresistance] OR [radiotherapy resistance] OR [sensitivity]). The reports selected up to August 17, 2022 were included. There were no restrictions with regard to the type of studies or the language used.

Inclusion and exclusion criteria

Studies fulfilling the following criteria were included: (1) original research studies in which the role of host-derived regulatory ncRNAs (miRNA, lncRNA, or circRNA) in bone or soft-tissue sarcoma was investigated; and (2) studies examining the role of ncRNAs in therapeutic drug or radiation resistance. Investigations on exogenous regulatory RNAs or non-original research articles, such as review articles, conference proceedings, editorials, and book chapters, were excluded.

Titles and abstracts were independently screened for relevance by the two authors of this study (HHC and TZ), while disagreements were resolved through discussions with a third author (FYZ).

Data extraction

The following data were extracted: first author and year of publication, pathological type of sarcoma, type of study, ncRNA class investigated, therapeutic agents used, methods used to detect the corresponding ncRNA, number of replicates/specimens (for *in vitro* and *in vivo* studies) or patients (for clinical studies), gene or cellular pathways involved, and major conclusions.

Quality assessment

The quality of the included studies was assessed using the Würzburg Methodological Quality Score (W-MeQS; [Uçeyler et al., 2011](#)). W-MeQS consists of 12 items that are relevant for assessing the quality of a laboratory method. This tool contains 12 items that assess selection bias, performance bias, attrition bias, detection bias, reporting bias, reagents status, charts status, and measurements status. These factors are commonly involved *in vitro* and *in vivo* studies. The higher the W-MeQS score, the better the quality of the study. For each item fulfilled, one point is given, and the score is the total sum of all points achieved, so the maximum score achievable is 12. If the target of interest was measured by just one method, this score marks the end score. If more than one method was used, a sub-score is calculated for each method as described, and the end score is calculated as the mean of the sub-scores. The quality assessment was independently screened for relevance by two authors (HHC and TZ), and disagreements were resolved through discussions with a third author (FYZ).

Results

Summary of included studies and article quality

Our search strategy yielded 930 records. After eliminating duplicates, 927 records remained. Titles and abstracts were screened for content, and 738 underwent a full-text evaluation. The excluded studies were neither original articles nor directly related to sarcoma or lacked evidence of deregulation of the studied ncRNAs in sarcoma ([Supplementary file 3](#)). The reasons for exclusion and a flowchart of the processing steps are shown in [Figure 1](#). A total of 212 original studies investigating miRNAs, lncRNAs, or circRNAs in sarcomas were included. The selected studies were published between 2012 and 2022, with the exception of one published in 2009 and one published in 2010; our selection included *in vitro*, *in vivo*, and human studies. Of these, 178 articles examined the role of ncRNAs in chemotherapy-resistant sarcoma, 14 studied the role of ncRNAs in targeted therapy-resistant sarcoma, one focused on immune checkpoint inhibitor (ICI) resistance, six investigated radiotherapy resistance, and 13 evaluated the value of ncRNAs as biomarkers for predicting treatment response in sarcoma. Of the 212 included studies, 179 examined the role of ncRNAs in OS, 4 focused on chondrosarcoma, 3 on EWS, 2 on synovial sarcoma, and 16 on GIST. Moreover, 135, 54, and 23

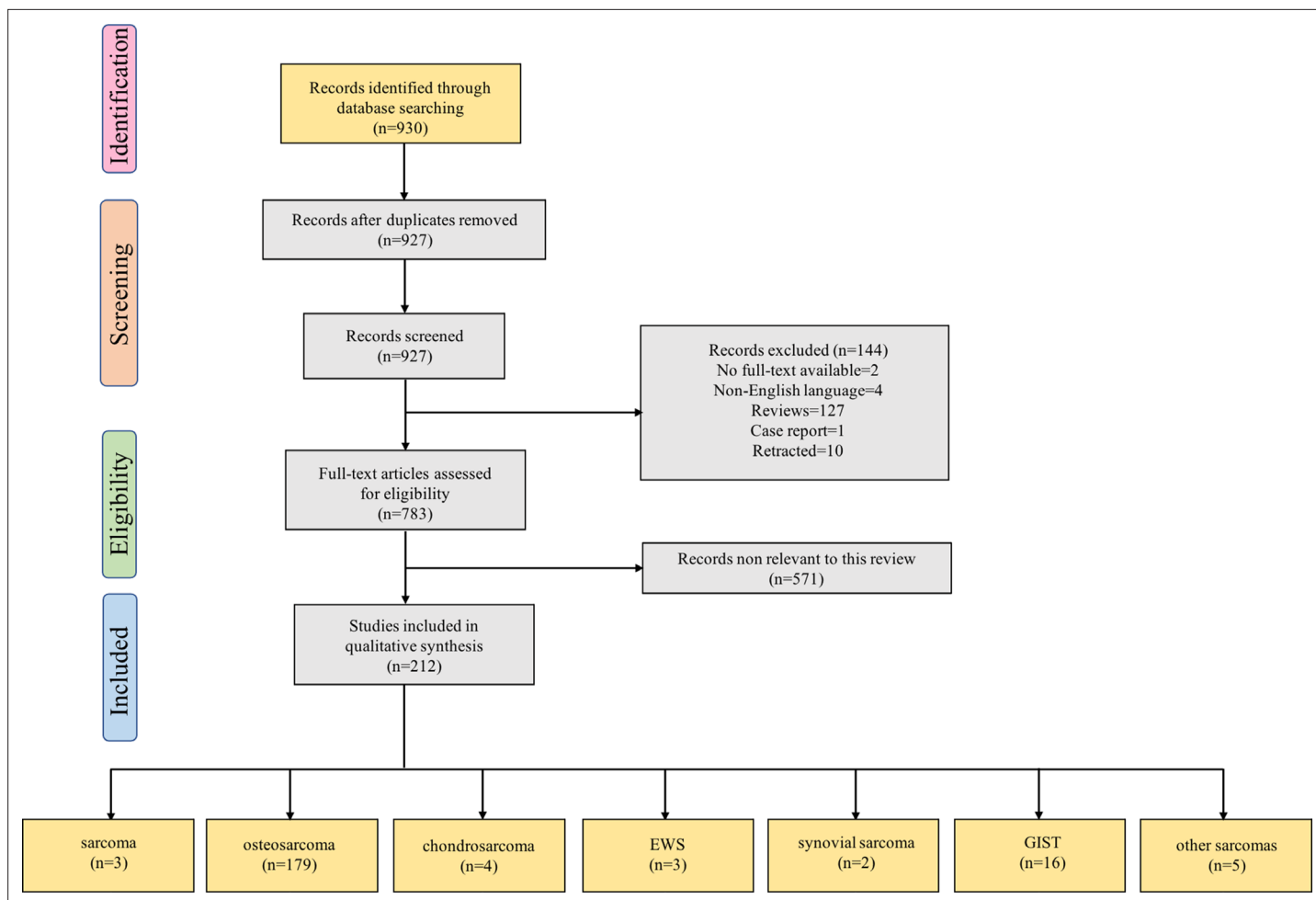


Figure 1. Flow diagram for Preferred Reporting Items for Systematic Reviews showing the literature selection process used to identify the studies included in the review. The last group of boxes show the number of studies on different pathological types of sarcomas. Among them, the box 'sarcoma' represents three studies focused on the role of non-coding RNAs in multiple pathological types of sarcoma. Moreover, the box 'other sarcomas' represents five studies focused on rhabdomyosarcoma, uterine leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and atypical teratoid/rhabdoid tumor. Abbreviations: EWS, Ewing's sarcoma; GIST, gastrointestinal stromal tumor.

studies were focused on miRNAs, lncRNAs, and circRNAs, respectively. **Supplementary file 1** lists all the ncRNAs investigated in different studies. The W-MeQS scores ranged from 3 to 10, with an average score of 5.42 (**Supplementary file 2**), implying that the study quality was compromised for most of the included articles. 95% of the articles had a quality score below 9; only 10 articles had a score of 9 or above. As most of the articles were based on animal or cell experiments, they exhibited obvious distribution bias, selection bias, and reporting bias. A summary of the molecular mechanisms underlying the actions of the ncRNAs associated with therapeutic resistance in sarcoma is shown in **Figure 2** and **Figure 3**.

ncRNAs participated in chemotherapy drug resistance

Osteosarcoma

Of the 179 articles that studied the role of ncRNAs in chemotherapy-resistant sarcoma, 166 focused on OS. Of these, 43 investigated the molecular regulatory mechanisms of lncRNAs in chemotherapeutic drug resistance in OS, 101 focused on miRNAs, 21 on circRNAs, and one study reported on both lncRNA MEG3 and hsa_circ_0001258 (Zhu *et al.*, 2019). Moreover, 19 overlapping ncRNAs were reported in more than one study, including four lncRNAs (lncRNA SNHG15 [Sun *et al.*, 2022; Zhang *et al.*, 2020a], lncRNA OIP5-AS1 [Song *et al.*, 2019; Liu and Wang, 2020; Sun *et al.*, 2020; Kun-Peng *et al.*, 2019], lncRNA TUG1 [Zhou *et al.*, 2020; Hu *et al.*, 2019], and

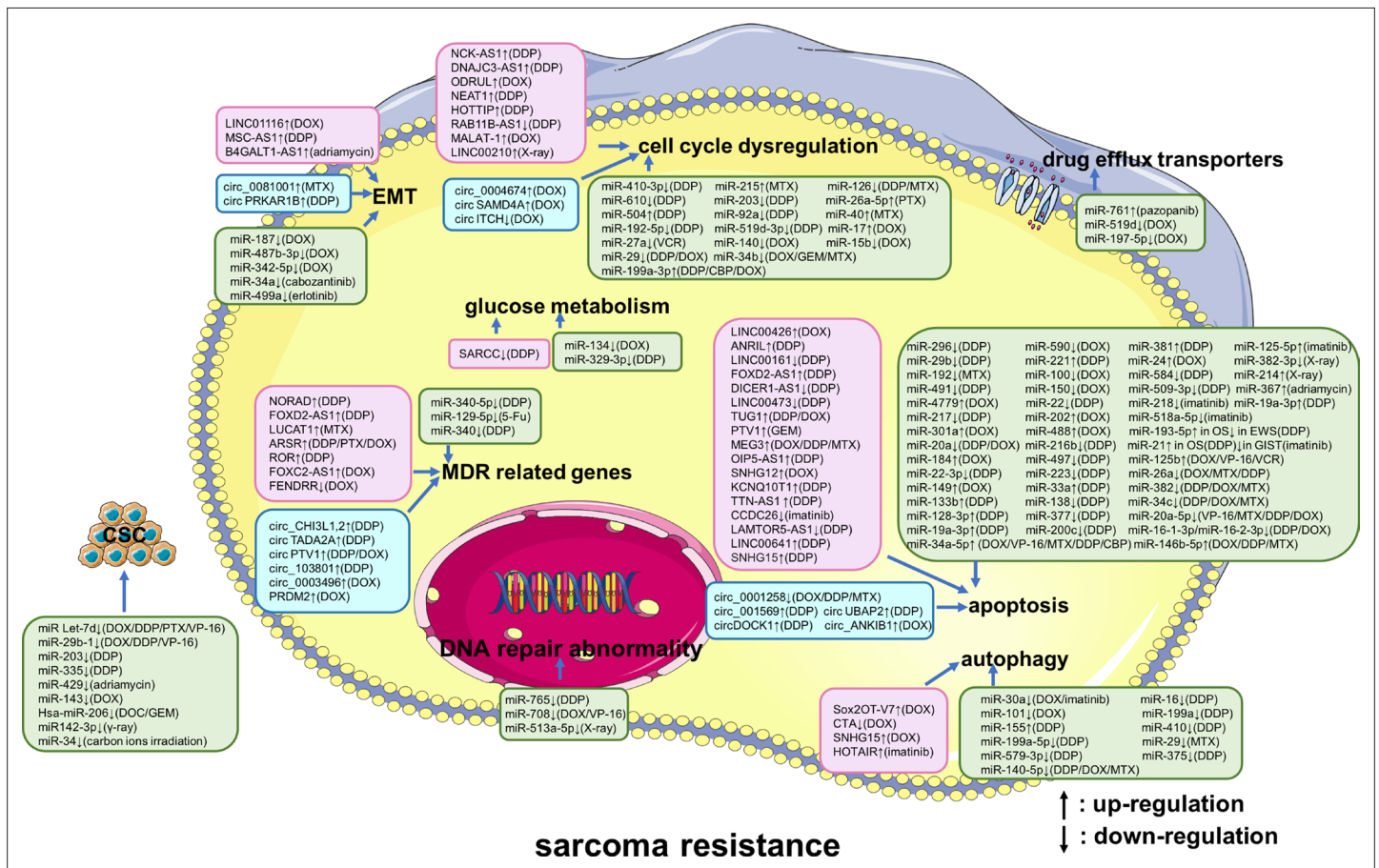


Figure 2. A summary diagram of miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) that participate in drug or radiation resistance in sarcoma. Several miRNAs, lncRNAs, and circRNAs have been found to be involved in sarcoma treatment resistance by influencing apoptosis, DNA repair, the cell cycle, glucose metabolism, autophagy, epithelial-mesenchymal transition, drug efflux, multiple drug resistance, and cancer stem cell behavior, through regulating the expression of potential target genes and related signaling pathways. These phenotypes are disordered in one or more sarcomas of different histological types, including osteosarcoma, chondrosarcoma, Ewing's sarcoma, synovial sarcoma, gastrointestinal stromal tumor, rhabdomyosarcoma, uterine leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and atypical teratoid/rhabdoid tumors. Specially, these phenotypes are all disordered in osteosarcoma. Abbreviations: 5-Fu, 5-fluorouracil; CBP, carboplatin; DDP, cisplatin; DOC, docetaxel; DOX, doxorubicin; GEM, gemcitabine; MTX, methotrexate; PTX, paclitaxel; VCR, vincristine; VP-16, etoposide.

lncRNA ANRIL [Li and Zhu, 2019b; Lee et al., 2021], 13 miRNAs (miR-29b [Luo et al., 2019; Li et al., 2020], miR-21 [Vanas et al., 2016; Ziyang and Yang, 2016], miR-22 [Wang et al., 2019c; Li et al., 2014; Meng et al., 2020a; Meng et al., 2020b; Zhou et al., 2018b], miR-199a-3p [Lei et al., 2018; Gao et al., 2015], miR-34a-5p [Pu et al., 2016; Pu et al., 2017b; Pu et al., 2017a], miR-34a [Li et al., 2017; Novello et al., 2014; Chen et al., 2016a], miR-140-5p [Wei et al., 2016; Meng et al., 2017], miR-203 [Chen et al., 2016a; Huang et al., 2021], miR-19a-3p [Zhang et al., 2019; Wang et al., 2022a], miR-140 [Song et al., 2009; Zhi et al., 2022], miR-29 [Osaki et al., 2016; Xu et al., 2018b], miR-221 [Yu et al., 2019; Zhao et al., 2013], and miR-100 [Xiao et al., 2017; Liu et al., 2016]), and two circRNAs (circPTV1 [Li et al., 2021c; Kun-Peng et al., 2018a; Wang et al., 2022c] and circRNA_0004674 [Ma et al., 2021; Bai et al., 2021]) (Table 1). The OS studies primarily focused on the molecular mechanisms of ncRNAs in cisplatin resistance (n=79), adriamycin/doxorubicin resistance (n=49), and multidrug resistance (MDR, n=27). The remaining 11 studies evaluated the role of ncRNAs in methotrexate (n=7), etoposide (n=1), paclitaxel (n=1), 5-fluorouracil (n=1), and gemcitabine (n=1) resistance in OS. From the 166 studies, we identified 82 ncRNAs that play important roles in enhancing chemoresistance in OS cells and/or animal models. Conversely, 84 ncRNAs had the opposite effect, contributing to chemotherapeutic sensitivity in OS (Supplementary file 4).

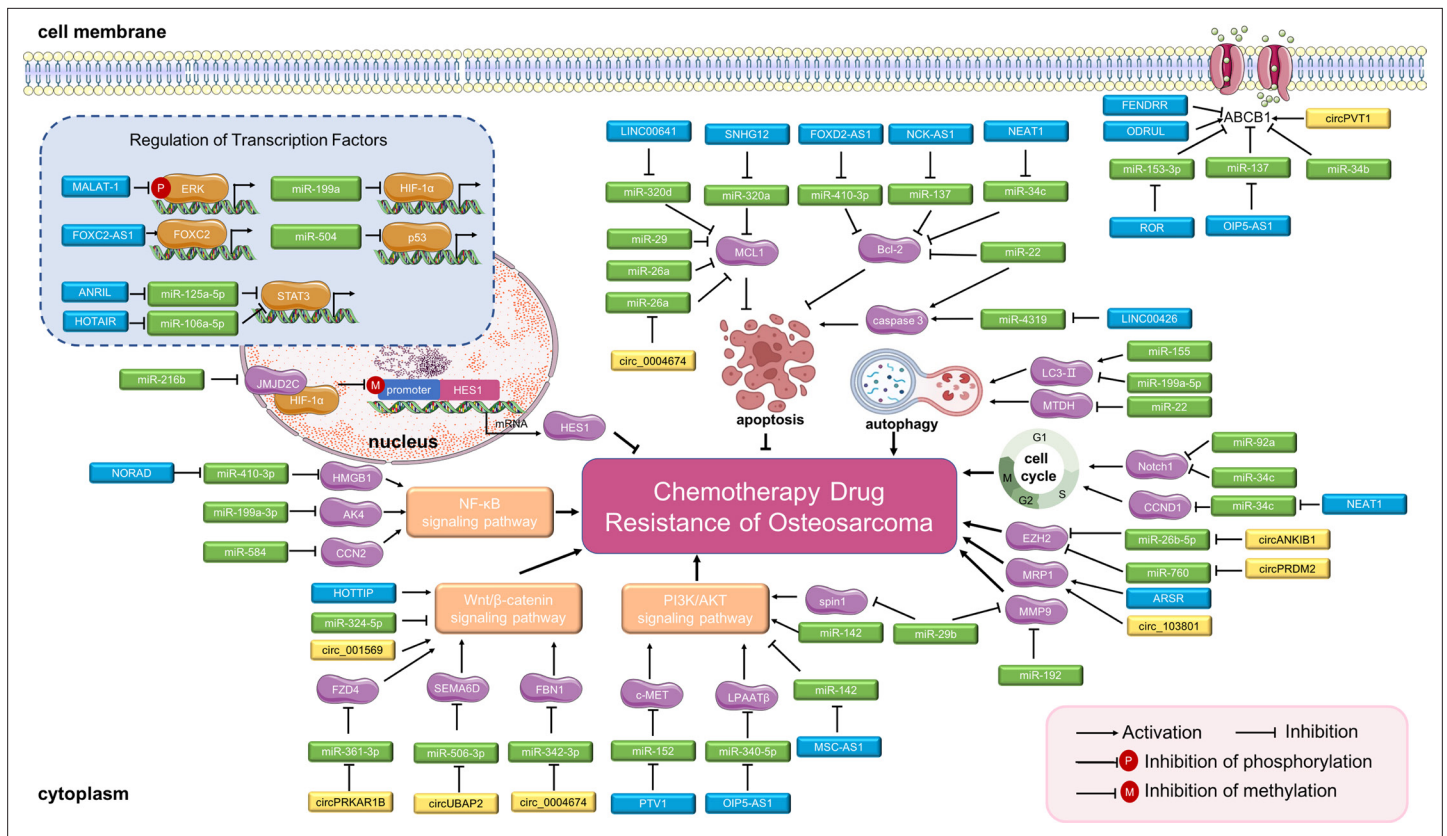


Figure 3. Long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and miRNAs in osteosarcoma chemoresistance. The main molecular mechanisms by which dysregulated ncRNAs (lncRNAs, circRNAs and miRNAs) mediate chemotherapy drug resistance in osteosarcoma are summarized. miRNAs usually bind directly to target genes and regulate their expression and related signaling pathways. lncRNAs and circRNAs can bind directly to target genes or can serve as miRNA sponges to regulate the expression of target genes and related signaling pathways, thereby mediating osteosarcoma chemoresistance. Abbreviations: ABCB1, ATP-binding cassette, subfamily B, member 1; AKT, protein kinase B; CCN2, CTGF, connective tissue growth factor; CCND1, cell cycle-related cyclin D1; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste 2 polycomb repressive complex 2; FBN1, fibrillin-1; FOXO2, forkhead box C2; HES1, hairy and enhancer of split-1; HIF-1 α , hypoxia-inducible factor-1; LPAAT β , lysophosphatidic acid acyltransferase; MCL1, myeloid cell leukemia 1; MMP-9, matrix metalloproteinase 9; MRP1, multidrug resistance-associated protein-1; MTDH, metadherin; NF- κ B, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3.

EWS and chondrosarcoma

Four studies reported the effects of miRNAs on chemotherapy treatment in EWS. Among these, one study demonstrated that miRNA-193a-5p controls cisplatin chemoresistance in both OS and EWS (Jacques et al., 2016). Two studies reported that miRNAs (miR-34a [Nakatani et al., 2012] and miR-708 [Robin et al., 2012]) increased tumor sensitivity to multiple drugs, including vincristine, doxorubicin, and etoposide, in EWS cells. One study showed that miR-125b overexpression reduced drug sensitivity in EWS cells (Iida et al., 2013). In addition, three studies investigated the role of miRNAs in the resistance of chondrosarcoma cells to chemotherapy; the results showed that miR-100 (Zhu et al., 2014), miR-23b (Huang et al., 2017), and miR-125b (Tang et al., 2016) increased cisplatin or doxorubicin sensitivity in chondrosarcoma cells.

Soft-tissue sarcoma

Among the remaining six studies, five reported that miRNAs (miR-27a [Bharathy et al., 2018], miR-22-3p [Xu et al., 2018a], miR-34a [Zhang et al., 2020b], miR-197-5p [Jain et al., 2022], and miR-206 [Li et al., 2021a]) enhanced sensitivity to the chemotherapeutic drugs vincristine, cisplatin, doxorubicin or gemcitabine in RMS, GIST, uterine leiomyosarcoma, and malignant fibrous histiocytoma (MFH), both *in vitro* and *in vivo*. By contrast, one study indicated that miR-17 promotes doxorubicin resistance in synovial sarcoma both *in vitro* and *in vivo* (Minami et al., 2014).

Table 1. The targets of non-coding RNAs (ncRNAs) that regulate therapeutic resistance in sarcoma.

Therapeutic strategies	Themes	No. of studies	ncRNA frequently involved	Key genes or pathways involved
Chemotherapy				
	Studies of long ncRNAs (lncRNAs)	43	lncRNA SNHG15, lncRNA OIP5-AS1, lncRNA TUG1, and lncRNA ANRIL	NF- κ B, STAT3, PI3K/AKT, Bax, Bcl-2, caspase3, cleaved caspase3, ABCB1, and MCL1
	Studies on miRNAs	101	miR-29b, miR-21, miR-22, miR-199a-3p, miR-34a-5p, miR-34a, miR-140-5 p, miR-203, miR-19a-3p, miR-140, miR-29, miR-221, and miR-100	MMP-9, KRAS, Bcl-2, PI3K/AKT, NF- κ B, c-Myc, LC3- I , LC3- II , HIF-1 α , MCL1, North1, Wnt/ β -catenin, mTOR, p53, and SOX2
Osteosarcomas (OS)	Studies on circular RNAs (circRNAs)	21	circPTV1 and circRNA_0004674	Wnt/ β -catenin, EZH2
Other sarcomas	Studies on ncRNAs	13	Various	p53, and AKT
Targeted therapy				
Gastrointestinal stromal tumors (GIST)	Studies on lncRNAs	4	lncRNA CCDC26	
	Studies on miRNAs	6	miR-125a-5p	Various
Other sarcomas	Studies on miRNAs	4	Various	Various
Immunotherapy				
Sarcomas	Studies on lncRNAs	1	Various	N/A
Radiotherapy				
Sarcomas	Studies on ncRNAs	6	Various	Various
Biomarker				
Sarcomas	Studies on ncRNAs	13	Various	N/A

ncRNAs participated in resistance to targeted therapy drugs

Of the 14 studies that investigated role of ncRNAs in targeted therapy resistance, three focused on the role of miRNAs in OS resistance to targeted therapy drugs. Their *in vitro* and *in vivo* results showed that miR-34a (Wang et al., 2021), miR-596 (Wang et al., 2019a), and miR-499a (Wang et al., 2019b) enhanced the sensitivity of OS to cabozantinib, anlotinib, and erlotinib, respectively. In addition, ten studies illustrated the effects of ncRNAs in GISTs treated with imatinib. Four of the 10 studies demonstrated that the lncRNA CCDC26 (Cao et al., 2018; Yan et al., 2019) reduced the resistance, whereas HOTAIR (Zhang et al., 2021a) and RP11-616M22.7 (Shao et al., 2021) enhanced the resistance of GISTs to imatinib *in vitro* and/or *in vivo* by regulating different downstream targets (the c-KIT, ATG2B, IGF-1R, and Hippo signaling pathways). The other six studies reported the roles of different miRNAs in GISTs treated with imatinib: four miRNAs (miR-218 [Fan et al., 2015], miR-30a [Chen et al., 2020a], miR-518-5p [Shi et al., 2016], and miR-21 [Cao et al., 2016]) sensitized GIST cells and/or animal models to imatinib, whereas two miRNAs (miR-125-5p [Huang et al., 2018; Akçakaya et al., 2014] and miR-107 [Akçakaya et al., 2014]) enhanced imatinib resistance in GIST cells. Two overlapping ncRNAs, lncRNA CCDC26 (Cao et al., 2018; Yan et al., 2019) and miR-125-5p (Huang et al., 2018; Akçakaya et al., 2014), were reported in more than one study. Moreover, the remaining studies showed that miR-761 enhanced pazopanib resistance in synovial sarcoma cells (Shiozawa et al., 2018).

lncRNAs participated in ICI resistance

Only one study met our criteria for ncRNAs in sarcoma resistance to immunotherapy. One bioinformatic analysis reported that the overexpression of the lncRNAs ADAM6, C5orf58, CXCR2P1, FCGR2C, HCP5, HLA-H, NAPS, NCF1B, and NCF1C reduced the sensitivity of sarcoma to ICIs (Pang and Hao, 2021).

ncRNAs participated in radioresistance

Among the six studies focused on the radiosensitivity of sarcoma, four focused on the sensitivity of OS to X-rays. One study demonstrated that LINC00210 (He et al., 2020) reduced the sensitivity of

OS cells to this therapy, and another study showed that miR-214 (Li et al., 2019a) induced OS radio-resistance both *in vitro* and *in vivo*. Two studies found that miRNAs (miR-328-3p [Yang et al., 2018] and miR-513a-5p [Dai et al., 2018]) could directly lead to the radiosensitization of OS cells and animal tumor models. Furthermore, one study reported that rapamycin combined with an miR-34 mimic may overcome the carbon ion irradiation resistance of high-grade chondrosarcoma (Vares et al., 2020). The remaining study demonstrated that miR-142-3 p overexpression significantly increased the radio-sensitivity of atypical teratoid/rhabdoid tumor (ATRT) cells (Lee et al., 2014).

ncRNAs as biomarkers for predicting treatment response

Twelve articles evaluated ncRNAs as biomarkers but none of them included an external validation cohort. Six studies identified the role of ncRNAs (lncRNA growth arrest-specific 5 [Polvani et al., 2022], lncRNA ENST00000563280 [Zhu et al., 2015], miR-21 [Yuan et al., 2012], miR-125b [Luo et al., 2016], hsa_circ_0008336 [Han et al., 2020], hsa_circ_0004664 [Han et al., 2020], hsa_circ_0003302 [Han et al., 2020], and hsa_circ_0004674 [Kun-Peng et al., 2018b]) as biomarkers for predicting chemotherapeutic response in OS. Among the ncRNAs in these studies, the presence of circulating miR-125b was able to distinguish chemotherapy-resistant OS from chemotherapy-sensitive OS with an AUC value of 0.793, and sensitivity and specificity levels of 76.9 and 79.1%, respectively (Luo et al., 2016). Moreover, five studies in patients with GISTs focused on differences in the expression of lncRNAs and miRNAs between pre-imatinib/imatinib-sensitive serum or tissues and imatinib-resistant serum or tissues. One of the five reported miR-518e-5p as a potential biomarker for secondary imatinib resistance with an AUC value of 0.9938 and sensitivity and specificity values of 99.8 and 82.1%, respectively (Kou et al., 2018). Finally, one study reported that the expression level of the lncRNA HAR1B was higher in pazopanib responders among patients with bone and soft-tissue sarcomas, indicating that HAR1B may serve as a predictive biomarker for response to pazopanib treatment (Yamada et al., 2021).

Target genes, signaling pathways, and functions of ncRNAs

The genes and molecular pathways targeted by ncRNAs that are involved in the regulation of therapeutic resistance in sarcoma are summarized in Table 1. The majority of targets identified in the literature search were members of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), Wnt/ β -catenin, and NF- κ B signaling pathways. The most commonly identified targets were ABCB1 (lncRNA LUCAT1 [Han and Shi, 2018], lncRNA ODRUL [Zhang et al., 2016], lncRNA ROR [Cheng et al., 2019b]), lncRNA FENDRR (Kun Peng et al., 2017), lncRNA FOXC2-AS1 (Zhang et al., 2017b), STAT3 (lncRNA ANRIL [Li and Zhu, 2019b]), lncRNA HOTAIR (Guo et al., 2020), Bax and Bcl-2 (lncRNA FOXD2-AS1 [Zhang et al., 2021b]), lncRNA NCK-AS1 (Cheng et al., 2019a), and lncRNA NEAT1 (Hu et al., 2018). In addition, ncRNAs targeted MCL1 both directly (lncRNA SNHG12 [Zhou et al., 2018a], miR-29 [Osaki et al., 2016], and miR-26a [Li and Ma, 2021b]) and indirectly (LINC00641 [Tang et al., 2022b] via miR-320d), targeted EZH2 both directly (miR-138 [Zhu et al., 2016]) and indirectly (circ_ANKIB1 [Tang et al., 2022a] via miR-26b-5p), and targeted p53 both directly (miR-34a [Nakatani et al., 2012], miR-504 [Chen et al., 2019], and miR-125b [Iida et al., 2013]) and indirectly (miR-590 [Long and Lin, 2019] via ATM). ncRNAs also targeted MMP-9 (miR-29b [Luo et al., 2019] and miR-192 [Bazavar et al., 2020]), KRAS (miR-192 [Bazavar et al., 2020] and miR-217 [Zhang et al., 2015]), c-Myc (miR-192 [Bazavar et al., 2020] and miR-34a [Li et al., 2017]), LC3- I and LC3- II (miR-101 [Chang et al., 2014], miR-155 [Chen et al., 2014], and miR-199a-5p [Li et al., 2016a]), HIF-1 α (miR-199a [Keremu et al., 2019] and miR-216b [Yang et al., 2020]), North1 (miR-34c [Xu et al., 2014] and miR-92a [Liu et al., 2018]), SOX2 (miR-429 [Zhang et al., 2020e] and miR-29b-1 [Di Fiore et al., 2014]), and caspase 3 (LINC00426 [Wang et al., 2020a] and the lncRNA NEAT1 [Hu et al., 2018]). The majority of commonly expressed ncRNAs were involved in epithelial-to-mesenchymal transition (EMT), cancer stem cells (CSCs), cell cycle dysregulation, glucose metabolism, multi-drug resistance (MDR)-related genes, DNA repair abnormality, apoptosis, autophagy, and drug efflux transporters (Figure 2 and Figure 3).

Discussion

This systematic review summarized the reports on the molecular mechanisms underlying the involvement of ncRNAs in drug and radiotherapy resistance in bone and soft-tissue sarcomas published over the past decade. Our aim, to identify common factors in the dysregulation of ncRNAs that are associated with therapeutic resistance in sarcoma, may provide clues about the mechanisms underlying this resistance. However, only a few overlapping ncRNAs were reported in two or more studies focusing on chemotherapy resistance in OS and targeted therapy resistance in GIST. Moreover, we found that the downstream targets of ncRNAs were predominantly found in the PI3K/AKT, Wnt/ β -catenin, and NF- κ B pathways. We also described the differential expression of ncRNAs between chemoresistant and chemosensitive sarcoma tissues and/or cells, which may support the potential of ncRNAs as biomarkers for predicting the sarcoma effect. Here, we further discuss some of the key findings from the studies included in this review and delineate some major limitations and potential prospects.

ncRNAs in chemoresistance of OS

High-dose methotrexate with leukovorin-rescue, ifosfamide, doxorubicin, and cisplatin are considered the most active agents for OS treatment (*Cortes et al., 1974; Smrke et al., 2021*), but drug resistance is still the main cause of disease progression and recurrence. Resistance to chemotherapy in sarcoma can be linked to perturbations of the mechanisms that underlie signal transduction, cell death (apoptosis and autophagy), MDR-related gene expression, and transcriptional factor regulation (*Lilienthal and Herold, 2020*). There is evidence supporting the role of perturbed signal transduction pathways, such as the PI3K/AKT, Wnt/ β -catenin, and NF- κ B pathways, in the development of chemotherapy resistance in OS. It has been shown that components of the PI3K/AKT signaling pathway are frequently altered in human cancers and that these changes may contribute decisively to the resistant phenotype (*Fresno Vara et al., 2004*). ncRNAs affect the sensitivity of OS cells by targeting PI3K/AKT signaling directly or indirectly. c-MET, a receptor for hepatocyte growth factor, has been reported to promote tumorigenicity in a variety of cancers (*Wu et al., 2017*). For instance, lncRNAPT1 promoted gemcitabine resistance in OS cells by activating PI3K/AKT signaling via c-MET (*Sun et al., 2019*). miR-221 also promoted cisplatin resistance in OS cells by directly activating PI3K/AKT (*Zhao et al., 2013*). Spindlin 1 (spin1), a new member of the SPIN/SSTY family, has been shown to promote tumorigenesis in human cancers (*Fang et al., 2018*). By contrast, miR-29b increased doxorubicin sensitivity in OS through inhibition of PI3K/AKT signaling by regulating spin1 expression (*Li et al., 2020*). Moreover, aberrant activation of Wnt/ β -catenin signaling is tightly linked with therapy response in various cancers (*Zhang and Wang, 2020c*). Studies included in our review also demonstrated that ncRNAs regulate resistance to chemotherapy drugs by regulating Wnt/ β -catenin signaling. For example, lncRNA HOTTIP (*Li et al., 2016b*), circ_001569 (*Zhang et al., 2018*), and circPRKAR1B (*Feng et al., 2021*) promoted drug resistance by activating Wnt/ β -catenin signaling. Among these ncRNAs, the lncRNA HOTTIP (*Li et al., 2016b*) and circ_001569 (*Zhang et al., 2018*) targeted Wnt/ β -catenin directly. Frizzled class receptor 4 (FZD4), a class Frizzled G-protein-coupled receptor (GPCR), is also a WNT receptor (*El-Sehemy et al., 2020*). CircPRKAR1 activated Wnt/ β -catenin by sponging miR-361-3 p, and thus upregulated the expression of FZD4 (*Feng et al., 2021*). By contrast, miR-342-5 p sensitized OS cells to doxorubicin by inhibiting the expression of both Wnt7b and β -catenin (*Liu et al., 2019*). In addition, emerging studies indicate that dysregulation of the NF- κ B pathway causes cancers (*Yu et al., 2020*) and enhances drug resistance in tumor cells (*Mirzaei et al., 2022*). The ncRNAs can potentially function as upstream mediators and modulate NF- κ B in OS. At the molecular level, *Xie et al., 2020* indicated that the lncRNA NORAD (Non-coding RNA-activated by DNA damage) promoted the cisplatin resistance of OS by sponging miR-410-3 p and thus activating NF- κ B. By contrast, miR-410-3 p promoted the drug sensitivity in OS cells by downregulating high-mobility group box-1 (HMGB1) and, subsequently, inhibiting NF- κ B activity (*Wang et al., 2020b*).

In addition to the abnormal activation of key signal transduction pathways, alterations in cell death signaling may also contribute to chemotherapy resistance in OS. ncRNAs have been found to participate in OS chemoresistance by regulating apoptosis-related proteins, such as Bcl-2, Bax, caspase 3, and MCL1. It has been reported that overexpression of the anti-apoptotic protein Bcl-2 in malignant cells fortifies their drug-resistance capacity (*Hafezi and Rahmani, 2021*). Conversely, the upregulation of the pro-apoptotic proteins Bax and caspase-3, and of the activated form cleaved caspase-3, plays the opposite role in human cancers (*Hafezi and Rahmani, 2021; Fulda, 2015*).

For instance, the lncRNA NCK-AS1 was found to be upregulated in cisplatin-resistance OS cell lines. At the molecular level, the lncRNA NCK-AS1 enhanced drug resistance in OS by upregulating Bcl-2 and downregulating Bax and cleaved caspase-3 through the sponging of miR-137 (Cheng et al., 2019a). Hu et al., 2018 reported that the lncRNA NEAT1 also promoted cisplatin-resistance in both OS cells and a xenograft model by upregulating Bcl-2 and downregulating Bax via miR-34c. Myeloid cell leukemia-1 (MCL1), an antiapoptotic member of the BCL2 family, contributes to cell survival and resistance to diverse chemotherapeutic agents in human cancers (Sancho et al., 2022). The study conducted by Zhou et al., 2018a showed that the lncRNA SNHG12 enhanced doxorubicin-resistance in OS cells by positively regulating the expression of MCL1 by sponging miR-320a. Moreover, circ_0004674 facilitated OS progression and doxorubicin resistance by upregulating MCL1 via miR-142-5p (Ma et al., 2021). By contrast, miR-26a reversed MDR in OS cells, and when xenografted in nude mice, it directly inhibited the expression of MCL1 (Li and Ma, 2021b). In addition, the regulation of autophagy-related proteins, including HMGB1, LC3- I , and LC3- II , by ncRNAs also played important roles in OS chemoresistance. The chromatin-binding nuclear protein HMGB1 plays a role in facilitating autophagy following the administration of cytotoxic agents (Tang et al., 2010). It has been reported that overexpression of HMGB1 in OS cell lines allowed them to resist autophagy when treated with doxorubicin, cisplatin, and methotrexate (Huang et al., 2012). In addition, the overexpression of miR-22 hindered doxorubicin and cisplatin resistance in OS by inhibiting HMGB1-promoted autophagy *in vitro* (Li et al., 2014). LC3 and LC3 homologs enable autophagosomes that have the ability to bind autophagic substrates and/or proteins that mediate cargo selectivity (Galluzzi and Green, 2019), and it has been proved that the overexpression of LC3- II promoted autophagy and caused drug resistance in cancers (Wang et al., 2022b). Chen et al., 2014 found that overexpression of miR-155 significantly enhanced the conversion of LC3-I to LC3-II, promoted autophagy, and enhanced chemoresistance in OS. Conversely, miR-199-5 p reduced cisplatin resistance in OS cells by downregulating LC3- II and reducing the ratio of LC3- II to LC3- I (Li et al., 2016a).

Furthermore, abnormal expression of MDR-related proteins plays an important role in OS chemoresistance. The studies included in our review described the regulatory effect of ncRNAs on drug-resistance-related proteins, especially ATP-binding cassette subfamily B member 1 (ABCB-1), in OS. ABCB-1, a member of the ABC family of efflux transporters, is a classical MDR-related protein (Franke et al., 2010). The lncRNA FOXC2-AS1 may promote doxorubicin resistance in OS by facilitating ABCB1 expression via increasing the expression of the transcription factor FOXC2 (Zhang et al., 2017b). Overexpression of circPVT1 contributed to the doxorubicin and cisplatin resistance of OS cells by positively regulating ABCB-1 (Kun-Peng et al., 2018a). Conversely, miR-34b reversed drug resistance in OS by directly lowering the expression of ABCB-1 (Zhou et al., 2016). In addition, transcription factors such as p53 and HIF-1 α could be present downstream of ncRNAs and have been found to be involved in OS chemoresistance. Wild-type p53 is central for maintaining genomic stability and preventing oncogenesis, whereas mutant p53 is tightly associated with late-stage malignancy and drug resistance in cancers (Zhou et al., 2019). Wild-type p53-induced phosphatase 1 (WIP1), an oncogene that is overexpressed in diverse cancers, has been regarded as a critical inhibitor of the ataxia telangiectasia mutated (ATM)/radiation resistance gene 3 related (ATR)-p53DNA damage signaling pathway (Lu et al., 2008). In OS cells, miR-590 inhibited doxorubicin resistance by negatively regulating WIP1, and subsequently reduced the expression of both ATM and p53 (Long and Lin, 2019). It has been proved that the HIF family of hypoxia-inducible transcription factors is widely upregulated in human cancers. HIF-1 α has been associated with chemotherapy failure in various cancers (Rohwer and Cramer, 2011). Histone demethylase jumonji C domain-containing 2 C (JMJD2C) has been shown to serve as a co-activator for HIF-1 α in cancer progression (Luo et al., 2012). Yang et al., 2020 found that miR-216b enhanced cisplatin sensitivity in OS cells by downregulating JMJD2C and HIF-1 α , inhibiting the expression of the hairy and enhancer of split-1 (HES1) gene.

Collectively, ncRNAs play a key role in regulating OS chemoresistance, and therapeutic strategies that are based on small-molecule activator or inhibitor ncRNAs have the potential to rescue therapeutic resistance in patients with OS. Nevertheless, only a limited number of studies have illustrated the molecular mechanisms underlying the roles of ncRNAs in regulating OS chemoresistance; this aspect needs further research.

miRNAs in chemoresistance in EWS, chondrosarcoma, and soft-tissue sarcomas

EWS is an aggressive sarcoma of the bone and soft tissue that occurs at any age and has a 5-year overall survival rate of 65–75% for patients with localized disease and of <30% for those with metastases, except for those with isolated pulmonary metastasis for whom the 5-year survival rate is approximately 50% (Gaspar et al., 2015). Recent evidence highlighted that miRNAs were involved in various tumor processes related to chemoresistance in EWS, especially in regulating p53. For example, overexpression of miR-125b is associated with the downregulation of the pro-apoptotic molecules p53 and Bak, resulting in enhanced drug resistance in EWS (Iida et al., 2013). By contrast, a study performed by Nakatani et al., 2012 demonstrated that overexpression of miR-34a in wild-type p53 EWS cells decreased malignancy and increased tumor sensitivity in response to doxorubicin and vincristine.

Chondrosarcoma is the second most common primary malignant bone sarcoma, and usually exhibits resistance to chemotherapy (Zajac et al., 2021). miRNAs have been associated with reduced drug resistance in chondrosarcoma. For instance, the study conducted by Huang et al., 2017 showed that miR-23b increased cisplatin sensitivity in chondrosarcoma by inhibiting the Src-Akt pathway. Moreover, Tang et al., 2016 demonstrated that miR-125b acted as a tumor suppressor in chondrosarcoma cells by increasing doxorubicin sensitization by directly targeting the oncogene ErbB2, leading to the inhibition of glucose metabolism.

Soft-tissue sarcomas are rare tumors that account for 1% of all adult malignancies, with over 100 different histologic subtypes occurring predominately in the trunk, extremities, and retroperitoneum (Gamboa et al., 2020). The studies included in this review found that miRNAs participated in regulating chemoresistance in several soft-tissue sarcomas, such as RMS, fibrosarcoma and MFH. For instance, the PAX3:FOXO1 fusion oncogene mediated tolerance to chemotherapy in RMS (Singh et al., 2022). Bharathy et al., 2018 reported that overexpression of miR-27a led to PAX3:FOXO1 mRNA destabilization and chemotherapy sensitization in RMS both *in vitro* and *in vivo*. In fibrosarcoma, miR-197-5 p sensitizes HT1080 cells to doxorubicin by suppressing the expression of MDR genes, ABCC1, and major vault protein (MVP; Jain et al., 2022). Furthermore, miR-206 showed low levels of expression in docetaxel-resistant MFH cells. Mechanistically, miR-206 significantly inhibited MFH proliferative activity by regulating the properties of CSCs (Li et al., 2021a).

In summary, several biological mechanisms underlying bone and soft-tissue sarcomas involve ncRNAs, indicating that ncRNAs may be targets for therapies intended to overcome or prevent chemoresistance in sarcomas. For example, the inhibition of oncogenic ncRNAs and the activation of tumor-suppressive ncRNAs are promising therapeutic strategies for sarcoma treatment. Furthermore, a combination of targeted ncRNA therapy with conventional chemotherapy may effectively reverse sarcoma drug resistance and significantly improve the effects of chemotherapeutics, subsequently improving prognosis. Nevertheless, the studies focused on the regulatory role of ncRNAs in soft-tissue sarcoma are very limited. Thus, the implementation of therapies targeting specific ncRNAs to overcome drug resistance in sarcomas remains a challenge, and most ncRNAs have not been characterized for potential clinical applications. Therefore, further investigation and clinical trials are required to develop novel ncRNA-related therapeutic strategies to overcome drug resistance in sarcoma.

ncRNAs in resistance to targeted therapies in GIST and OS

GISTs are the most common subtype of soft-tissue sarcoma (Ducimetière et al., 2011). The targeted therapy drug imatinib is the gold standard therapy for GIST. This treatment has been found to prolong patient survival effectively, especially in the high-risk GIST group, as shown by a randomized trial study that included follow-up of 9.1 years (Casali, 2021). Therefore, imatinib resistance in GISTs is an important factor in disease progression and relapse. Recent studies have identified a vital role for ncRNAs in imatinib resistance in GIST. For example, ncRNAs may serve upstream of autophagy-related proteins (autophagy-related protein 2 homolog B [ATG2B] and Beclin1) in GIST and thus regulate drug sensitivity. At the molecular level, the lncRNA HOTAIR activated autophagy and promoted the imatinib resistance of GIST cells by increasing the expression of ATG2B via miR-130a (Zhang et al., 2021a). Inversely, miR-30a inactivated autophagy and sensitized GIST cells to imatinib by downregulating Beclin1 (Chen et al., 2020a). Moreover, it has been shown that members of the non-receptor protein tyrosine phosphatase (PTPN) family are differentially expressed in digestive tract cancers and are closely associated with improved disease prognosis (Chen et al., 2020b). With regard

to GIST, **Akçakaya et al., 2014** found that miR-125a-5p enhanced imatinib resistance by suppressing the expression of PTPN18.

In addition to the use of imatinib in GIST, targeted therapeutic drugs, the antiangiogenic agents anlotinib (**Wang et al., 2019a**), cabozantinib (**Wang et al., 2021**), and pazopanib (**Shiozawa et al., 2018**), and the epidermal growth factor receptor (EGFR) inhibitor erlotinib (**Wang et al., 2019b**) have also been used as rescue drugs after chemotherapy failure in OS. Several studies have investigated the mechanisms of resistance to targeted therapy involving ncRNAs in OS. For example, the Notch pathway is major regulator in human malignancies and also mediates drug resistance in cancer cells (**Zhang et al., 2017a**). **Wang et al., 2021** reported that miR-34a overexpression promoted the sensitivity of OS to cabozantinib by suppressing the Notch pathway. Moreover, SH3KBP1-binding protein 1 (SHKBP1) is an upstream molecule of EGFR that prevents EGFR degradation (**Liu et al., 2022**). The study conducted by **Wang et al., 2019b** found that the TGF β -miR-499a-SHKBP1 network orchestrates the EMT-associated kinase switch, which induces resistance to erlotinib in CD166⁺ OS CSC-like cells.

Overall, targeting of lncRNAs and miRNAs may be a promising strategy to improve the efficacy of sarcoma-targeted therapies. There have, however, been increasing concerns regarding the therapeutic potential of targeting a single ncRNA and other current targeting strategies. First, despite the numerous studies that have attempted to reveal the mechanisms and effects of ncRNAs, we have gained only superficial knowledge in the field, and the effects of circRNAs in sarcoma-targeted therapy remain largely unclear. Furthermore, given the large number of ncRNAs and their upregulation or downregulation in sarcoma, it is crucial to determine the most clinically relevant ncRNAs that have the greatest impact on disease outcome. Therefore, further studies are needed to investigate the mechanisms of ncRNA action in sarcoma-targeted drug resistance in order to improve patient survival.

lncRNAs in resistance of sarcomas to immunotherapy

Immunotherapy, which has been used for melanoma, is a new therapy paradigm that holds great promise for sarcoma treatment (**Falcone et al., 2020; Rutkowski et al., 2020**). Although the anti-CTLA-4 drug ipilimumab was well tolerated by patients with synovial sarcoma, no obvious efficacy was observed in this patient group (**Maki et al., 2013**). However, in a separate study using the anti-PD-1 antibody SARC028 to treat patients with bone sarcomas, a partial response was observed (**NCT02301039; Tawbi et al., 2017**). The primary resistance to immunotherapy may be caused by an immunosuppressive environment in which there is no pre-existing antitumor response (**Saleh and Elkord, 2020**). The overexpression of ICI molecules may create an immunosuppressive environment, leading to immunotherapy resistance in sarcoma. A previous study had found that the elevated expression of several lncRNAs was correlated with reduced immune cell infiltration and reduced sensitivity to ICIs in sarcomas (**Pang and Hao, 2021**). Despite disappointing results from preliminary immunotherapy trials for sarcomas, the combination of ICIs with cytotoxic chemotherapies or targeted therapies may significantly improve the prognosis for sarcoma patients.

Overall, immunotherapy is a promising strategy that requires specific adjustments for use in patients with sarcomas. More in-depth studies are needed to clarify the association between abnormal ncRNA expression and clinical efficacy of ICIs in sarcomas; for example, further investigations are needed to understand the changes in expression of ncRNAs that occur in the tumor tissue or serum of sarcoma patients treated with ICIs. Both *in vitro* and *in vivo* experiments are needed to investigate the molecular mechanisms underlying the influence of ncRNAs on ICI treatment in sarcomas. ncRNAs hold the potential to be used in predicting drug sensitivity and in improving treatment efficacy through the detection or perturbation of their expression, respectively, in patients with sarcoma who are undergoing immunotherapy.

ncRNAs in resistance of OS, chondrosarcoma, and ATRT to radiotherapy

Pre- and postoperative radiotherapy is widely used in sarcomas (**Haas, 2014**). Radiotherapy leads to the activation of an interconnected series of processes in the tumor microenvironment, including inflammation, cycling hypoxia, immunomodulation, revascularization, extracellular matrix remodeling coordinated by cancer-associated fibroblasts, and fibrosis. These changes affect the radiosensitivity

of cancer cells (Barker *et al.*, 2015). Moreover, many mechanisms for CSC radioresistance have been proposed, including drug efflux through ABC transporters, overactivation of the DNA damage response, apoptosis evasion, activation of the prosurvival pathway, cell cycle promotion, and/or cell metabolic alterations (García-Mayea *et al.*, 2020). In addition, the role of ncRNAs in radiotherapy resistance has been investigated in hepatocellular carcinoma, breast cancer, lung cancer, and gastric cancer (Zhang *et al.*, 2020d). Several studies have illustrated the molecular mechanisms through which ncRNAs regulate radiosensitivity in OS. For example, He *et al.*, 2020 demonstrated that knock-down of the lncRNA LINC00210 enhances the radiosensitivity of OS cells by acting as a miR-342-3 p sponge to positively regulate expression of the oncogene GDNF receptor alpha 1 (GFRA1). By contrast, overexpression of miR-328-3 p enhances the radiosensitivity of OS cells by directly targeting histone H2AX (Yang *et al.*, 2018). The effect of miR-34 and miR-142-3 p in radioresistance in chondrosarcoma (Vares *et al.*, 2020) and ATRT (Lee *et al.*, 2014) have been identified by regulating the transcription factors FOXO3 and SOX2, respectively. Specifically, overexpression of miR-34a enables chondrosarcoma cells to overcome resistance to carbon-ion irradiation by upregulating FOXO3, which leads to KLF4 repression (Vares *et al.*, 2020). Moreover, miR-142-3p was shown to reduce γ radiation resistance in pediatric brain ATRT by inhibiting expression of sex-determining region Y box 2 (SOX2) (Lee *et al.*, 2014).

In summary, targeting ncRNAs to overcome radiotherapy resistance in sarcomas is gaining interest; however, the number of studies cited in our review is still small. Further research is needed to explore the influence of additional ncRNAs on sarcoma radiotherapy. To select the most clinically effective target ncRNAs for reversing radiotherapy resistance, more in-depth *in vitro* and/or *in vivo* experimental studies as well as multi-center clinical studies with large samples, are urgently needed. In the future, interfering with the expression of ncRNAs may become an important strategy for improving the sensitivity of radiotherapy and the prognosis of patients with sarcoma.

ncRNAs as biomarkers for treatment monitoring

Sarcomas lack specific tumor markers. Although elevated lactate dehydrogenase levels, or more frequently alkaline phosphatase levels, in the serum have been found in some patients with OS, these serum indicators lack specificity and sensitivity. Therefore, the diagnosis and prognostic evaluation of diseases depend on imaging examinations and invasive biopsies (Ritter and Bielack, 2010). These methods are inconvenient for both primary screening of the disease and monitoring of short-term treatment outcomes. Hence, non-invasive biomarkers that have high sensitivity and specificity are required. Recently, exosomes, including tumor-associated proteins, enzymes, growth factors, bioactive lipids, miRNAs, and DNA sequences, have been considered as potential biomarkers for sarcoma diagnosis and prognosis evaluation, and as possible targets for sarcoma therapy (Min *et al.*, 2016). The differential expression of ncRNAs between drug-resistant and drug-sensitive sarcoma tissues or cells demonstrates the applicability of ncRNAs as biomarkers for prediction of treatment effect. In particular, a previous study reported that miR-518e-5p serves as a biomarker for imatinib resistance, showing high sensitivity (99.8%) and specificity (82.1%) with an AUC value of 0.9938 in GISTs (Kou *et al.*, 2018). A separate study reported an AUC value of 0.793 for miR-125b as a biomarker for predicting the chemosensitivity of OS, with a sensitivity of 76.9% and a specificity of 79.1%.

Overall, ncRNAs may have potential to serve as biomarkers for sarcoma drug resistance and to predict therapeutic responses in patients with sarcoma. However, because ncRNA detection can vary immensely depending on the method used, in-depth studies should focus on optimizing ncRNA detection methodology. Importantly, the results of the studies cited in this review may be biased, as most were single-center trials with small sample sizes. Therefore, further studies are needed to accelerate the clinical application of ncRNAs, and the inclusion of multi-center research studies will be particularly important in reducing the errors caused by differences between individual centers. In addition, the studies included in this review are mainly focused on lncRNAs and miRNAs, highlighting the lack of understanding of the role of circRNAs as biomarkers for the prediction of treatment effect in sarcoma and the need for further investigations. We expect future analysis of tumor-specific ncRNA biomarkers to offer not only improved diagnosis but also a convenient and sensitive method for monitoring the outcomes of treatments in sarcoma patients.

Conclusions

Despite the variability in the results of the studies examined, this systematic review supports the notion that ncRNAs have potential to be used as ideal biomarker candidates for treatment monitoring and future therapeutic targets in sarcomas. With further research, ncRNAs may become powerful compounds for sensitizing therapy-resistant sarcomas to standard treatments.

Acknowledgements

We would like to acknowledge the PubMed (MEDLINE) databases that supplied the literature retrieval library.

Additional information

Funding

Funder	Grant reference number	Author
345 Talent of Shengjing Hospital of China Medical University		Tao Zhang

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Author contributions

Huan-Huan Chen, Data curation, Writing - original draft, Writing - review and editing; Tie-Ning Zhang, Data curation, Software; Fang-Yuan Zhang, Conceptualization, Data curation, Software; Tao Zhang, Conceptualization, Data curation, Methodology, Writing - original draft

Author ORCIDs

Fang-Yuan Zhang  <http://orcid.org/0000-0002-1551-6048>

Tao Zhang  <http://orcid.org/0000-0001-5341-8249>

Decision letter and Author response

Decision letter <https://doi.org/10.7554/eLife.79655.sa1>

Author response <https://doi.org/10.7554/eLife.79655.sa2>

Additional files

Supplementary files

- Supplementary file 1. Summary of non-coding RNAs in sarcoma therapeutic resistance.
- Supplementary file 2. Quality assessment of the included studies according to Würzburg Methodological Quality Score (W-MeQS).
- Supplementary file 3. References of studies excluded in the systematic review (N=715).
- Supplementary file 4. Description of the 212 original studies of non-coding RNAs in sarcoma.
- MDAR checklist

Data availability

All data generated or analysed during this study are included in the manuscript and supporting file. The data has also been deposited to Dryad.

The following dataset was generated:

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Zhang T, Chen H, Zhang T, Zhang F	2022	212 original articles	https://dx.doi.org/10.5061/dryad.kd51c5b8t	Dryad Digital Repository, 10.5061/dryad.kd51c5b8t

References

- Akçakaya P**, Caramuta S, Åhlen J, Ghaderi M, Berglund E, Östman A, Bränström R, Larsson C, Lui WO. 2014. MicroRNA expression signatures of gastrointestinal stromal tumours: associations with imatinib resistance and patient outcome. *British Journal of Cancer* **111**:2091–2102. DOI: <https://doi.org/10.1038/bjc.2014.548>, PMID: 25349971
- Ashwal-Fluss R**, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N, Kadener S. 2014. CircRNA biogenesis competes with pre-mRNA splicing. *Molecular Cell* **56**:55–66. DOI: <https://doi.org/10.1016/j.molcel.2014.08.019>, PMID: 25242144
- Bai Y**, Li Y, Bai J, Zhang Y. 2021. Hsa_circ_0004674 promotes osteosarcoma doxorubicin resistance by regulating the mir-342-3p/FBN1 axis. *Journal of Orthopaedic Surgery and Research* **16**:510. DOI: <https://doi.org/10.1186/s13018-021-02631-y>, PMID: 34407841
- Barker HE**, Paget JTE, Khan AA, Harrington KJ. 2015. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nature Reviews. Cancer* **15**:409–425. DOI: <https://doi.org/10.1038/nrc3958>, PMID: 26105538
- Bazavar M**, Fazli J, Valizadeh A, Ma B, Mohammadi E, Asemi Z, Alemi F, Maleki M, Xing S, Yousefi B. 2020. MiR-192 enhances sensitivity of methotrexate drug to MG-63 osteosarcoma cancer cells. *Pathology - Research and Practice* **216**:153176. DOI: <https://doi.org/10.1016/j.prp.2020.153176>
- Bharathy N**, Berlow NE, Wang E, Abraham J, Settlemeyer TP, Hooper JE, Svalina MN, Ishikawa Y, Zientek K, Bajwa Z, Goros MW, Hernandez BS, Wolff JE, Rudek MA, Xu L, Anders NM, Pal R, Harrold AP, Davies AM, Ashok A, et al. 2018. The HDAC3–SMARCA4–mir-27a axis promotes expression of the pax3: foxo1 fusion oncogene in rhabdomyosarcoma. *Science Signaling* **11**:557. DOI: <https://doi.org/10.1126/scisignal.aau7632>
- Cao CL**, Niu HJ, Kang SP, Cong CL, Kang SR. 2016. miRNA-21 sensitizes gastrointestinal stromal tumors (gists) cells to imatinib via targeting B-cell lymphoma 2 (bcl-2). *European Review for Medical and Pharmacological Sciences* **20**:3574–3581 PMID: 27649657.
- Cao K**, Li M, Miao J, Lu X, Kang X, Zhu H, Du S, Li X, Zhang Q, Guan W, Dong Y, Xia X. 2018. CCDC26 knockdown enhances resistance of gastrointestinal stromal tumor cells to imatinib by interacting with c-kit. *American Journal of Translational Research* **10**:274–282 PMID: 29423012.
- Casali PG**. 2021. Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST). *Annals of Oncology: Journal of the European Society for Medical Oncology* **32**:533–541. DOI: <https://doi.org/10.1016/j.annonc.2021.01.004>, PMID: 33482247
- Chang Z**, Huo L, Li K, Wu Y, Hu Z. 2014. Blocked autophagy by mir-101 enhances osteosarcoma cell chemosensitivity in vitro. *TheScientificWorldJournal* **14**:794756. DOI: <https://doi.org/10.1155/2014/794756>, PMID: 25013866
- Chen L**, Jiang K, Jiang H, Wei P. 2014. Mir-155 mediates drug resistance in osteosarcoma cells via inducing autophagy. *Experimental and Therapeutic Medicine* **8**:527–532. DOI: <https://doi.org/10.3892/etm.2014.1752>, PMID: 25009614
- Chen X**, Chen XG, Hu X, Song T, Ou X, Zhang C, Zhang W, Zhang C. 2016a. Mir-34A and mir-203 inhibit survivin expression to control cell proliferation and survival in human osteosarcoma cells. *Journal of Cancer* **7**:1057–1065. DOI: <https://doi.org/10.7150/jca.15061>, PMID: 27326248
- Chen H**, Shen J, Choy E, Hornicek FJ, Duan Z. 2016b. Targeting protein kinases to reverse multidrug resistance in sarcoma. *Cancer Treatment Reviews* **43**:8–18. DOI: <https://doi.org/10.1016/j.ctrv.2015.11.011>, PMID: 26827688
- Chen X**, Lv C, Zhu X, Lin W, Wang L, Huang Z, Yang S, Sun J. 2019. MicroRNA-504 modulates osteosarcoma cell chemoresistance to cisplatin by targeting p53. *Oncology Letters* **17**:1664–1674. DOI: <https://doi.org/10.3892/ol.2018.9749>, PMID: 30675226
- Chen W**, Li Z, Liu H, Jiang S, Wang G, Sun L, Li J, Wang X, Yu S, Huang J, Dong Y. 2020a. MicroRNA-30a targets beclin-1 to inactivate autophagy and sensitizes gastrointestinal stromal tumor cells to imatinib. *Cell Death & Disease* **11**:198. DOI: <https://doi.org/10.1038/s41419-020-2390-7>, PMID: 32251287
- Chen J**, Zhao X, Yuan Y, Jing JJ. 2020b. The expression patterns and the diagnostic/prognostic roles of PTPN family members in digestive tract cancers. *Cancer Cell International* **20**:238. DOI: <https://doi.org/10.1186/s12935-020-01315-7>, PMID: 32536826
- Cheng Y**, Shen X, Zheng M, Zou G, Shen Y. 2019a. Knockdown of lncRNA NCK-AS1 regulates cisplatin resistance through modulating mir-137 in osteosarcoma cells. *OncoTargets and Therapy* **12**:11057–11068. DOI: <https://doi.org/10.2147/OTT.S228199>, PMID: 31908475
- Cheng FH**, Zhao ZS, Liu WD. 2019b. Long non-coding RNA ROR regulated ABCB1 to induce cisplatin resistance in osteosarcoma by sponging mir-153-3p. *European Review for Medical and Pharmacological Sciences* **23**:7256–7265. DOI: https://doi.org/10.26355/eurrev_201909_18828, PMID: 31539112
- Chillón I**, Marcia M. 2020. The molecular structure of long non-coding RNAs: emerging patterns and functional implications. *Critical Reviews in Biochemistry and Molecular Biology* **55**:662–690. DOI: <https://doi.org/10.1080/10409238.2020.1828259>, PMID: 33043695
- Cho WCS**. 2010. MicroRNAs: potential biomarkers for cancer diagnosis, prognosis and targets for therapy. *The International Journal of Biochemistry & Cell Biology* **42**:1273–1281. DOI: <https://doi.org/10.1016/j.biocel.2009.12.014>, PMID: 20026422
- Cortes EP**, Holland JF, Wang JJ, Sinks LF, Blom J, Senn H, Bank A, Glidewell O. 1974. Amputation and adriamycin in primary osteosarcoma. *The New England Journal of Medicine* **291**:998–1000. DOI: <https://doi.org/10.1056/NEJM197411072911903>, PMID: 4528415

- Dai N**, Qing Y, Cun Y, Zhong Z, Li C, Zhang S, Shan J, Yang X, Dai X, Cheng Y, Xiao H, Xu C, Li M, Wang D. 2018. MiR-513a-5p regulates radiosensitivity of osteosarcoma by targeting human apurinic/apyrimidinic endonuclease. *Oncotarget* **9**:25414–25426. DOI: <https://doi.org/10.18632/oncotarget.11003>, PMID: 29875998
- Di Fiore R**, Drago-Ferrante R, Pentimalli F, Di Marzo D, Forte IM, D'Anneo A, Carlisi D, De Blasio A, Giuliano M, Tesoriere G, Giordano A, Vento R. 2014. MicroRNA-29b-1 impairs in vitro cell proliferation, self-renewal and chemoresistance of human osteosarcoma 3AB-OS cancer stem cells. *International Journal of Oncology* **45**:2013–2023. DOI: <https://doi.org/10.3892/ijo.2014.2618>, PMID: 25174983
- Ducimetière F**, Lurkin A, Ranchère-Vince D, Decouvlaere AV, Péoc'h M, Istier L, Chalabreysse P, Muller C, Alberti L, Bringuier PP, Scoazec JY, Schott AM, Bergeron C, Cellier D, Blay JY, Ray-Coquard I. 2011. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLOS ONE* **6**:e20294. DOI: <https://doi.org/10.1371/journal.pone.0020294>, PMID: 21826194
- El-Sehemy A**, Selvadurai H, Ortin-Martinez A, Pokrajac N, Mamatjan Y, Tachibana N, Rowland K, Lee L, Park N, Aldape K, Dirks P, Wallace VA. 2020. Notch mediates tumor-promoting and -suppressive effects in glioblastoma via Notch and Wnt. *The Journal of Clinical Investigation* **130**:3069–3086. DOI: <https://doi.org/10.1172/JCI128994>, PMID: 32182224
- Falcone I**, Conciatori F, Bazzichetto C, Ferretti G, Cognetti F, Ciuffreda L, Milella M. 2020. Tumor microenvironment: implications in melanoma resistance to targeted therapy and immunotherapy. *Cancers* **12**:10. DOI: <https://doi.org/10.3390/cancers12102870>, PMID: 33036192
- Fan R**, Zhong J, Zheng S, Wang Z, Xu Y, Li S, Zhou J, Yuan F. 2015. MicroRNA-218 increase the sensitivity of gastrointestinal stromal tumor to imatinib through PI3K/Akt pathway. *Clinical and Experimental Medicine* **15**:137–144. DOI: <https://doi.org/10.1007/s10238-014-0280-y>, PMID: 24706111
- Fang Z**, Cao B, Liao JM, Deng J, Plummer KD, Liao P, Liu T, Zhang W, Zhang K, Li L, Margolin D, Zeng SX, Xiong J, Lu H. 2018. SPIN1 promotes tumorigenesis by blocking the ul18 (universal large ribosomal subunit protein 18) -MDM2-p53 pathway in human cancer. *eLife* **7**:e31275. DOI: <https://doi.org/10.7554/eLife.31275>, PMID: 29547122
- Feng ZH**, Zheng L, Yao T, Tao SY, Wei XA, Zheng ZY, Zheng BJ, Zhang XY, Huang B, Liu JH, Chen YL, Shan Z, Yuan PT, Wang CG, Chen J, Shen SY, Zhao FD. 2021. EIF4A3-induced circular RNA PRKAR1B promotes osteosarcoma progression by mir-361-3p-mediated induction of FZD4 expression. *Cell Death & Disease* **12**:1025. DOI: <https://doi.org/10.1038/s41419-021-04339-7>, PMID: 34716310
- Franke RM**, Gardner ER, Sparreboom A. 2010. Pharmacogenetics of drug transporters. *Current Pharmaceutical Design* **16**:220–230. DOI: <https://doi.org/10.2174/138161210790112683>, PMID: 19835554
- Fresno Vara JA**, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. 2004. PI3K/Akt signalling pathway and cancer. *Cancer Treatment Reviews* **30**:193–204. DOI: <https://doi.org/10.1016/j.ctrv.2003.07.007>, PMID: 15023437
- Fu D**, Lu C, Qu X, Li P, Chen K, Shan L, Zhu X. 2019. Lncrna TTN-AS1 regulates osteosarcoma cell apoptosis and drug resistance via the mir-134-5p/MBTD1 axis. *Aging* **11**:8374–8385. DOI: <https://doi.org/10.18632/aging.102325>, PMID: 31600142
- Fulda S**. 2015. Targeting apoptosis for anticancer therapy. *Seminars in Cancer Biology* **31**:84–88. DOI: <https://doi.org/10.1016/j.semcancer.2014.05.002>, PMID: 24859747
- Galluzzi L**, Green DR. 2019. Autophagy-independent functions of the autophagy machinery. *Cell* **177**:1682–1699. DOI: <https://doi.org/10.1016/j.cell.2019.05.026>, PMID: 31199916
- Gamboa AC**, Gronchi A, Cardona K. 2020. Soft-Tissue sarcoma in adults: an update on the current state of histiotype-specific management in an era of personalized medicine. *CA* **70**:200–229. DOI: <https://doi.org/10.3322/caac.21605>, PMID: 32275330
- Gao Y**, Feng Y, Shen JK, Lin M, Choy E, Cote GM, Harmon DC, Mankin HJ, Hornicek FJ, Duan Z. 2015. Cd44 is a direct target of miR-199a-3p and contributes to aggressive progression in osteosarcoma. *Scientific Reports* **5**:11365. DOI: <https://doi.org/10.1038/srep11365>, PMID: 26079799
- Garcia-Mayea Y**, Mir C, Masson F, Paciucci R, LLeonart ME. 2020. Insights into new mechanisms and models of cancer stem cell multidrug resistance. *Seminars in Cancer Biology* **60**:166–180. DOI: <https://doi.org/10.1016/j.semcancer.2019.07.022>, PMID: 31369817
- Gaspar N**, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley M-C, Kovar H, Grimer R, Whelan J, Claude L, Delattre O, Paulussen M, Picci P, Sundby Hall K, van den Berg H, Ladenstein R, Michon J, Hjorth L, Judson I, Luksch R, et al. 2015. Ewing sarcoma: current management and future approaches through collaboration. *Journal of Clinical Oncology* **33**:3036–3046. DOI: <https://doi.org/10.1200/JCO.2014.59.5256>, PMID: 26304893
- Guo J**, Dou D, Zhang T, Wang B. 2020. Hotair promotes cisplatin resistance of osteosarcoma cells by regulating cell proliferation, invasion, and apoptosis via mir-106a-5p/STAT3 axis. *Cell Transplantation* **29**:963689720948447. DOI: <https://doi.org/10.1177/0963689720948447>, PMID: 32757663
- Haas RLM**. 2014. Present and future of radiotherapy before and after surgery for sarcoma patients. *European Journal of Surgical Oncology* **40**:1595–1597. DOI: <https://doi.org/10.1016/j.ejso.2014.10.002>, PMID: 25454829
- Hafezi S**, Rahmani M. 2021. Targeting Bcl-2 in cancer: advances, challenges, and perspectives. *Cancers* **13**:1292. DOI: <https://doi.org/10.3390/cancers13061292>, PMID: 33799470
- Han Z**, Shi L. 2018. Long non-coding RNA LUCAT1 modulates methotrexate resistance in osteosarcoma via miR-200c/ABC1 axis. *Biochemical and Biophysical Research Communications* **495**:947–953. DOI: <https://doi.org/10.1016/j.bbrc.2017.11.121>, PMID: 29170124

- Han J, Ye Z, Kong Q, Wu F, Wang G, Wang K. 2020. Circular RNA expression pattern in cisplatin-resistant osteosarcoma cells. *Translational Cancer Research* **9**:262–270. DOI: <https://doi.org/10.21037/tcr.2019.12.80>, PMID: 35117180
- Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. 2013. Natural RNA circles function as efficient microRNA sponges. *Nature* **495**:384–388. DOI: <https://doi.org/10.1038/nature11993>, PMID: 23446346
- He P, Xu YQ, Wang ZJ, Sheng B. 2020. Lncrna LINC00210 regulated radiosensitivity of osteosarcoma cells via mir-342-3p/GFRA1 axis. *Journal of Clinical Laboratory Analysis* **34**:e23540. DOI: <https://doi.org/10.1002/jcla.23540>, PMID: 32841458
- Hentze MW, Preiss T. 2013. Circular RNAs: splicing's enigma variations. *The EMBO Journal* **32**:923–925. DOI: <https://doi.org/10.1038/emboj.2013.53>, PMID: 23463100
- Hu Y, Yang Q, Wang L, Wang S, Sun F, Xu D, Jiang J. 2018. Knockdown of the oncogene lncRNA NEAT1 restores the availability of miR-34c and improves the sensitivity to cisplatin in osteosarcoma. *Bioscience Reports* **38**:BSR20180375. DOI: <https://doi.org/10.1042/BSR20180375>, PMID: 29654165
- Hu T, Fei Z, Su H, Xie R, Chen L. 2019. Polydatin inhibits proliferation and promotes apoptosis of doxorubicin-resistant osteosarcoma through lncRNA TUG1 mediated suppression of Akt signaling. *Toxicology and Applied Pharmacology* **371**:55–62. DOI: <https://doi.org/10.1016/j.taap.2019.04.005>, PMID: 30974157
- Huang J, Ni J, Liu K, Yu Y, Xie M, Kang R, Vernon P, Cao L, Tang D. 2012. Hmgb1 promotes drug resistance in osteosarcoma. *Cancer Research* **72**:230–238. DOI: <https://doi.org/10.1158/0008-5472.CAN-11-2001>, PMID: 22102692
- Huang K, Chen J, Yang MS, Tang YJ, Pan F. 2017. Inhibition of Src by microRNA-23b increases the cisplatin sensitivity of chondrosarcoma cells. *Cancer Biomarkers* **18**:231–239. DOI: <https://doi.org/10.3233/CBM-160102>, PMID: 28085008
- Huang W-K, Akçakaya P, Gangaev A, Lee L, Zeljic K, Hajeri P, Berglund E, Ghaderi M, Åhlén J, Bränström R, Larsson C, Lui W-O. 2018. MiR-125a-5p regulation increases phosphorylation of FAK that contributes to imatinib resistance in gastrointestinal stromal tumors. *Experimental Cell Research* **371**:287–296. DOI: <https://doi.org/10.1016/j.yexcr.2018.08.028>, PMID: 30149002
- Huang Z, Huang L, Liu L, Wang L, Lin W, Zhu X, Su W, Lv C. 2021. Knockdown of microRNA-203 reduces cisplatin chemo-sensitivity to osteosarcoma cell lines MG63 and U2OS in vitro by targeting runx2. *Journal of Chemotherapy* **33**:328–341. DOI: <https://doi.org/10.1080/1120009X.2021.1899441>, PMID: 33764270
- Hulshoff MS, Del Monte-Nieto G, Kovacic J, Krenning G. 2019. Non-Coding RNA in endothelial-to-mesenchymal transition. *Cardiovascular Research* **115**:1716–1731. DOI: <https://doi.org/10.1093/cvr/cvz211>, PMID: 31504268
- Iida K, Fukushi J-I, Matsumoto Y, Oda Y, Takahashi Y, Fujiwara T, Fujiwara-Okada Y, Hatano M, Nabashima A, Kamura S, Iwamoto Y. 2013. Mir-125B develops chemoresistance in Ewing sarcoma/primitive neuroectodermal tumor. *Cancer Cell International* **13**:21. DOI: <https://doi.org/10.1186/1475-2867-13-21>, PMID: 23497288
- Jacques C, Calleja LR, Baud'huin M, Quillard T, Heymann D, Lamoureux F, Ory B. 2016. MiRNA-193a-5p repression of p73 controls cisplatin chemoresistance in primary bone tumors. *Oncotarget* **7**:54503–54514. DOI: <https://doi.org/10.18632/oncotarget.10950>, PMID: 27486986
- Jain N, Das B, Mallick B. 2022. MiR-197-5p increases doxorubicin-mediated anticancer cytotoxicity of HT1080 fibrosarcoma cells by decreasing drug efflux. *DNA Repair* **109**:103259. DOI: <https://doi.org/10.1016/j.dnarep.2021.103259>, PMID: 34871862
- Keremu A, Aini A, Maimaitirexiati Y, Liang Z, Aila P, Xierela P, Tusun A, Moming H, Yusufu A. 2019. Overcoming cisplatin resistance in osteosarcoma through the mir-199a-modulated inhibition of HIF-1 α . *Bioscience Reports* **39**:BSR20170080. DOI: <https://doi.org/10.1042/BSR20170080>, PMID: 28442599
- Kou Y, Yang R, Wang Q. 2018. Serum mir-518e-5p is a potential biomarker for secondary imatinib-resistant gastrointestinal stromal tumor. *Journal of Biosciences* **43**:1015–1023. DOI: <https://doi.org/10.1007/s12038-018-9805-y>, PMID: 30541960
- Kung JTY, Colognori D, Lee JT. 2013. Long noncoding RNAs: past, present, and future. *Genetics* **193**:651–669. DOI: <https://doi.org/10.1534/genetics.112.146704>, PMID: 23463798
- Kun Peng Z, Xiao-Long M, Chun-Lin Z. 2017. Lncrna FENDRR sensitizes doxorubicin-resistance of osteosarcoma cells through down-regulating ABCB1 and ABCC1. *Oncotarget* **8**:71881–71893. DOI: <https://doi.org/10.18632/oncotarget.17985>, PMID: 29069754
- Kun-Peng Z, Xiao-Long M, Chun-Lin Z. 2018a. Overexpressed circpvt1, a potential new circular RNA biomarker, contributes to doxorubicin and cisplatin resistance of osteosarcoma cells by regulating ABCB1. *International Journal of Biological Sciences* **14**:321–330. DOI: <https://doi.org/10.7150/ijbs.24360>, PMID: 29559849
- Kun-Peng Z, Xiao-Long M, Lei Z, Chun-Lin Z, Jian-Ping H, Tai-Cheng Z. 2018b. Screening circular RNA related to chemotherapeutic resistance in osteosarcoma by RNA sequencing. *Epigenomics* **10**:1327–1346. DOI: <https://doi.org/10.2217/epi-2018-0023>, PMID: 30191736
- Kun-Peng Z, Chun-Lin Z, Xiao-Long M, Lei Z. 2019. Fibronectin-1 modulated by the long noncoding RNA OIP5-AS1/mir-200b-3p axis contributes to doxorubicin resistance of osteosarcoma cells. *Journal of Cellular Physiology* **234**:6927–6939. DOI: <https://doi.org/10.1002/jcp.27435>, PMID: 30204936
- Lee YY, Yang YP, Huang MC, Wang ML, Yen SH, Huang PI, Chen YW, Chiou SH, Lan YT, Ma HI, Shih YH, Chen MT. 2014. MicroRNA142-3p promotes tumor-initiating and radioresistant properties in malignant pediatric brain tumors. *Cell Transplantation* **23**:669–690. DOI: <https://doi.org/10.3727/096368914X678364>, PMID: 24816458

- Lee AM**, Ferdjallah A, Moore E, Kim DC, Nath A, Greengard E, Huang RS. 2021. Long non-coding RNA ANRIL as a potential biomarker of chemosensitivity and clinical outcomes in osteosarcoma. *International Journal of Molecular Sciences* **22**:20. DOI: <https://doi.org/10.3390/ijms222011168>, PMID: 34681828
- Lei W**, Yan C, Ya J, Yong D, Yujun B, Kai L. 2018. Mir-199A-3P affects the multi-chemoresistance of osteosarcoma through targeting AK4. *BMC Cancer* **18**:631. DOI: <https://doi.org/10.1186/s12885-018-4460-0>, PMID: 29866054
- Li X**, Wang S, Chen Y, Liu G, Yang X. 2014. Mir-22 targets the 3' UTR of HMGB1 and inhibits the HMGB1-associated autophagy in osteosarcoma cells during chemotherapy. *Tumour Biology* **35**:6021–6028. DOI: <https://doi.org/10.1007/s13277-014-1797-0>, PMID: 24609901
- Li Z**, Huang C, Bao C, Chen L, Lin M, Wang X, Zhong G, Yu B, Hu W, Dai L, Zhu P, Chang Z, Wu Q, Zhao Y, Jia Y, Xu P, Liu H, Shan G. 2015. Exon-Intron circular RNAs regulate transcription in the nucleus. *Nature Structural & Molecular Biology* **22**:256–264. DOI: <https://doi.org/10.1038/nsmb.2959>, PMID: 25664725
- Li Y**, Jiang W, Hu Y, Da Z, Zeng C, Tu M, Deng Z, Xiao W. 2016a. MicroRNA-199a-5p inhibits cisplatin-induced drug resistance via inhibition of autophagy in osteosarcoma cells. *Oncology Letters* **12**:4203–4208. DOI: <https://doi.org/10.3892/ol.2016.5172>, PMID: 27895792
- Li Z**, Zhao L, Wang Q. 2016b. Overexpression of long non-coding RNA HOTTIP increases chemoresistance of osteosarcoma cell by activating the wnt/ β -catenin pathway. *American Journal of Translational Research* **8**:2385–2393 PMID: 27347346.
- Li QC**, Xu H, Wang X, Wang T, Wu J. 2017. MiR-34A increases cisplatin sensitivity of osteosarcoma cells in vitro through up-regulation of c-myc and bim signal. *Cancer Biomarkers* **21**:135–144. DOI: <https://doi.org/10.3233/CBM-170452>, PMID: 29060932
- Li Y**, Song X, Liu Z, Li Q, Huang M, Su B, Mao Y, Wang Y, Mo W, Chen H. 2019a. Upregulation of mir-214 induced radioresistance of osteosarcoma by targeting PHLDA2 via PI3K/akt signaling. *Frontiers in Oncology* **9**:298. DOI: <https://doi.org/10.3389/fonc.2019.00298>
- Li G**, Zhu Y. 2019b. Effect of lncrna ANRIL knockdown on proliferation and cisplatin chemoresistance of osteosarcoma cells in vitro. *Pathology, Research and Practice* **215**:931–938. DOI: <https://doi.org/10.1016/j.prp.2019.01.042>, PMID: 30777616
- Li S**, Bai H, Chen X, Gong S, Xiao J, Li D, Li L, Jiang Y, Li T, Qin X, Yang H, Wu C, You F, Liu Y. 2020. Soft substrate promotes osteosarcoma cell self-renewal, differentiation, and drug resistance through miR-29b and its target protein spin 1. *ACS Biomaterials Science & Engineering* **6**:5588–5598. DOI: <https://doi.org/10.1021/acsbiomaterials.0c00816>, PMID: 33320589
- Li D**, Zhao K, Zhao Z, Jiang B, Gong X, Zhang Y, Guo Y, Xiao H, Wang Y, Liu H, Yi C, Gu W. 2021a. High expression microrna-206 inhibits the growth of tumor cells in human malignant fibrous histiocytoma. *Frontiers in Cell and Developmental Biology* **9**:751833. DOI: <https://doi.org/10.3389/fcell.2021.751833>, PMID: 34900997
- Li M**, Ma W. 2021b. Mir-26A reverses multidrug resistance in osteosarcoma by targeting MCL1. *Frontiers in Cell and Developmental Biology* **9**:645381. DOI: <https://doi.org/10.3389/fcell.2021.645381>, PMID: 33816494
- Li D**, Huang Y, Wang G, Zhao F. 2021c. Circular RNA circpvt1 contributes to doxorubicin (dxr) resistance of osteosarcoma cells by regulating TRIAP1 via mir-137. *BioMed Research International* **2021**:1–19. DOI: <https://doi.org/10.1155/2021/7463867>, PMID: 33981772
- Lilienthal I**, Herold N. 2020. Targeting molecular mechanisms underlying treatment efficacy and resistance in osteosarcoma: a review of current and future strategies. *International Journal of Molecular Sciences* **21**:18. DOI: <https://doi.org/10.3390/ijms21186885>, PMID: 32961800
- Liu Y**, Zhu ST, Wang X, Deng J, Li WH, Zhang P, Liu BS. 2016. MiR-100 inhibits osteosarcoma cell proliferation, migration, and invasion and enhances chemosensitivity by targeting IGFIR. *Technology in Cancer Research & Treatment* **15**:40–48. DOI: <https://doi.org/10.1177/1533034615601281>, PMID: 26306402
- Liu Q**, Song Y, Duan X, Chang Y, Guo J. 2018. MiR-92A inhibits the progress of osteosarcoma cells and increases the cisplatin sensitivity by targeting notch1. *BioMed Research International* **2018**:9870693. DOI: <https://doi.org/10.1155/2018/9870693>, PMID: 29984257
- Liu Q**, Wang Z, Zhou X, Tang M, Tan W, Sun T, Deng Y. 2019. MiR-342-5p inhibits osteosarcoma cell growth, migration, invasion, and sensitivity to doxorubicin through targeting wnt7b. *Cell Cycle* **18**:3325–3336. DOI: <https://doi.org/10.1080/15384101.2019.1676087>, PMID: 31601147
- Liu L**, Wang S. 2020. Long non-coding RNA OIP5-AS1 knockdown enhances CDDP sensitivity in osteosarcoma via mir-377-3p/FOSL2 axis. *OncoTargets and Therapy* **13**:3853–3866. DOI: <https://doi.org/10.2147/OTT.S232918>, PMID: 32440152
- Liu Q**, Li H, Yang M, Mei Y, Niu T, Zhou Z, Zhang X, He X, Wang L, Li J. 2022. Suppression of tumor growth and metastasis in shkbp1 knockout mice. *Cancer Gene Therapy* **29**:709–721. DOI: <https://doi.org/10.1038/s41417-021-00349-x>, PMID: 34112919
- Long X**, Lin XJ. 2019. P65-mediated mir-590 inhibition modulates the chemoresistance of osteosarcoma to doxorubicin through targeting wild-type p53-induced phosphatase 1. *Journal of Cellular Biochemistry* **120**:5652–5665. DOI: <https://doi.org/10.1002/jcb.27849>, PMID: 30387173
- Lu X**, Nguyen TA, Moon SH, Darlington Y, Sommer M, Donehower LA. 2008. The type 2C phosphatase Wip1: an oncogenic regulator of tumor suppressor and DNA damage response pathways. *Cancer Metastasis Reviews* **27**:123–135. DOI: <https://doi.org/10.1007/s10555-008-9127-x>, PMID: 18265945
- Luo W**, Chang R, Zhong J, Pandey A, Semenza GL. 2012. Histone demethylase JMJD2C is a coactivator for hypoxia-inducible factor 1 that is required for breast cancer progression. *PNAS* **109**:E3367–E3376. DOI: <https://doi.org/10.1073/pnas.1217394109>, PMID: 23129632

- Luo Z, Liu M, Zhang H, Xia Y. 2016. Association of circulating miR-125b and survival in patients with osteosarcoma-A single center experience. *Journal of Bone Oncology* **5**:167–172. DOI: <https://doi.org/10.1016/j.jbo.2016.06.002>, PMID: 28008378
- Luo DJ, Li LJ, Huo HF, Liu XQ, Cui HW, Jiang DM. 2019. MicroRNA-29B sensitizes osteosarcoma cells to doxorubicin by targeting matrix metalloproteinase 9 (MMP-9) in osteosarcoma. *European Review for Medical and Pharmacological Sciences* **23**:1434–1442. DOI: https://doi.org/10.26355/eurrev_201902_17100, PMID: 30840264
- Ma XL, Zhan TC, Hu JP, Zhang CL, Zhu KP. 2021. Doxorubicin-induced novel circrna_0004674 facilitates osteosarcoma progression and chemoresistance by upregulating MCL1 through mir-142-5p. *Cell Death Discovery* **7**:309. DOI: <https://doi.org/10.1038/s41420-021-00694-8>, PMID: 34689155
- Maki RG, Jungbluth AA, Gnjatic S, Schwartz GK, D'Adamo DR, Keohan ML, Wagner MJ, Scheu K, Chiu R, Ritter E, Kachel J, Lowy I, Old LJ, Ritter G. 2013. A pilot study of anti-CTLA4 antibody ipilimumab in patients with synovial sarcoma. *Sarcoma* **1**:168145. DOI: <https://doi.org/10.1155/2013/168145>
- Meng Y, Gao R, Ma J, Zhao J, Xu E, Wang C, Zhou X. 2017. MicroRNA-140-5p regulates osteosarcoma chemoresistance by targeting HMGN5 and autophagy. *Scientific Reports* **7**:416. DOI: <https://doi.org/10.1038/s41598-017-00405-3>, PMID: 28341864
- Meng CY, Zhao ZQ, Bai R, Zhao W, Wang YX, Sun L, Sun C, Feng W, Guo SB. 2020a. MicroRNA-22 regulates autophagy and apoptosis in cisplatin resistance of osteosarcoma. *Molecular Medicine Reports* **22**:3911–3921. DOI: <https://doi.org/10.3892/mmr.2020.11447>, PMID: 33000186
- Meng CY, Zhao ZQ, Bai R, Zhao W, Wang YX, Xue HQ, Sun L, Sun C, Feng W, Guo SB. 2020b. MicroRNA-22 mediates the cisplatin resistance of osteosarcoma cells by inhibiting autophagy via the PI3K/akt/mTOR pathway. *Oncology Reports* **43**:1169–1186. DOI: <https://doi.org/10.3892/or.2020.7492>, PMID: 32323781
- Min L, Shen J, Tu C, Hornicek F, Duan Z. 2016. The roles and implications of exosomes in sarcoma. *Cancer Metastasis Reviews* **35**:377–390. DOI: <https://doi.org/10.1007/s10555-016-9630-4>, PMID: 27342745
- Minami Y, Kohsaka S, Tsuda M, Yachi K, Hatori N, Tanino M, Kimura T, Nishihara H, Minami A, Iwasaki N, Tanaka S. 2014. SS18-SSX-regulated miR-17 promotes tumor growth of synovial sarcoma by inhibiting p21WAF1/CIP1. *Cancer Science* **105**:1152–1159. DOI: <https://doi.org/10.1111/cas.12479>, PMID: 24989082
- Mirzaei S, Saghari S, Bassiri F, Raesi R, Zarrabi A, Hushmandi K, Sethi G, Tergaonkar V. 2022. NF- κ B as a regulator of cancer metastasis and therapy response: a focus on epithelial-mesenchymal transition. *Journal of Cellular Physiology* **237**:2770–2795. DOI: <https://doi.org/10.1002/jcp.30759>, PMID: 35561232
- Nacev BA, Jones KB, Intlekofer AM, Yu JSE, Allis CD, Tap WD, Ladanyi M, Nielsen TO. 2020. The epigenomics of sarcoma. *Nature Reviews. Cancer* **20**:608–623. DOI: <https://doi.org/10.1038/s41568-020-0288-4>, PMID: 32782366
- Nakatani F, Ferracin M, Manara MC, Ventura S, Del Monaco V, Ferrari S, Alberghini M, Grilli A, Knuutila S, Schaefer K-L, Mattia G, Negrini M, Picci P, Serra M, Scotlandi K. 2012. Mir-34A predicts survival of Ewing's sarcoma patients and directly influences cell chemo-sensitivity and malignancy. *The Journal of Pathology* **226**:796–805. DOI: <https://doi.org/10.1002/path.3007>, PMID: 21960059
- Novello C, Pazzaglia L, Conti A, Quattrini I, Pollino S, Perego P, Picci P, Benassi MS. 2014. P53-Dependent activation of microRNA-34a in response to etoposide-induced DNA damage in osteosarcoma cell lines not impaired by dominant negative p53 expression. *PLOS ONE* **9**:e114757. DOI: <https://doi.org/10.1371/journal.pone.0114757>, PMID: 25490093
- Osaki S, Tazawa H, Hasei J, Yamakawa Y, Omori T, Sugiu K, Komatsubara T, Fujiwara T, Sasaki T, Kunisada T, Yoshida A, Urata Y, Kagawa S, Ozaki T, Fujiwara T. 2016. Ablation of MCL1 expression by virally induced microRNA-29 reverses chemoresistance in human osteosarcomas. *Scientific Reports* **6**:28953. DOI: <https://doi.org/10.1038/srep28953>, PMID: 27356624
- Pang B, Hao Y. 2021. Integrated analysis of the transcriptome profile reveals the potential roles played by long noncoding RNAs in immunotherapy for sarcoma. *Frontiers in Oncology* **11**:690486. DOI: <https://doi.org/10.3389/fonc.2021.690486>, PMID: 34178688
- Polvani S, Martignano F, Scoccianti G, Pasqui A, Palomba AR, Conticello S, Galli A, Palchetti I, Caporalini C, Antonuzzo L, Campanacci DA, Pillozzi S. 2022. Growth arrest-specific 5 lncRNA as a valuable biomarker of chemoresistance in osteosarcoma. *Anti-Cancer Drugs* **33**:278–285. DOI: <https://doi.org/10.1097/CAD.0000000000001263>, PMID: 35045526
- Pu Y, Zhao F, Wang H, Cai W, Gao J, Li Y, Cai S. 2016. MiR-34a-5p promotes the multi-drug resistance of osteosarcoma by targeting the CD117 gene. *Oncotarget* **7**:28420–28434. DOI: <https://doi.org/10.18632/oncotarget.8546>, PMID: 27056900
- Pu Y, Zhao F, Li Y, Cui M, Wang H, Meng X, Cai S. 2017a. The mir-34a-5p promotes the multi-chemoresistance of osteosarcoma via repression of the AGTR1 gene. *BMC Cancer* **17**:45. DOI: <https://doi.org/10.1186/s12885-016-3002-x>, PMID: 28073349
- Pu Y, Zhao F, Wang H, Cai S. 2017b. MiR-34a-5p promotes multi-chemoresistance of osteosarcoma through down-regulation of the d11 gene. *Scientific Reports* **7**:44218. DOI: <https://doi.org/10.1038/srep44218>, PMID: 28281638
- Ritter J, Bielack SS. 2010. Osteosarcoma. *Annals of Oncology* **21 Suppl 7**:vii320–vii325. DOI: <https://doi.org/10.1093/annonc/mdq276>, PMID: 20943636
- Robin TP, Smith A, McKinsey E, Reaves L, Jedlicka P, Ford HL. 2012. Ews/Fli1 regulates Eya3 in Ewing sarcoma via modulation of mirna-708, resulting in increased cell survival and chemoresistance. *Molecular Cancer Research* **10**:1098–1108. DOI: <https://doi.org/10.1158/1541-7786.MCR-12-0086>, PMID: 22723308

- Rohwer N**, Cramer T. 2011. Hypoxia-Mediated drug resistance: novel insights on the functional interaction of HIFs and cell death pathways. *Drug Resistance Updates* **14**:191–201. DOI: <https://doi.org/10.1016/j.drug.2011.03.001>, PMID: 21466972
- Rutkowski P**, Indini A, De Luca M, Merelli B, Mariuk-Jarema A, Teterycz P, Rogala P, Lugowska I, Cybulska-Stopa B, Labianca A, Di Guardo L, Del Vecchio M, Pigozzo J, Randon G, Corti F, Tondini CA, Rulli E, Mandala M. 2020. Body mass index (BMI) and outcome of metastatic melanoma patients receiving targeted therapy and immunotherapy: a multicenter international retrospective study. *Journal for Immunotherapy of Cancer* **8**:e001117. DOI: <https://doi.org/10.1136/jitc-2020-001117>, PMID: 33203662
- Saleh R**, Elkord E. 2020. Acquired resistance to cancer immunotherapy: role of tumor-mediated immunosuppression. *Seminars in Cancer Biology* **65**:13–27. DOI: <https://doi.org/10.1016/j.semcancer.2019.07.017>, PMID: 31362073
- Sancho M**, Leiva D, Lucendo E, Orzáez M. 2022. Understanding MCL1: from cellular function and regulation to pharmacological inhibition. *The FEBS Journal* **289**:6209–6234. DOI: <https://doi.org/10.1111/febs.16136>, PMID: 34310025
- Shao Y**, Lian S, Zheng J, Tong H, Wang J, Xu J, Liu W, Hu G, Zhang Y, He J. 2021. RP11-616M22.7 recapitulates imatinib resistance in gastrointestinal stromal tumor. *Molecular Therapy. Nucleic Acids* **25**:264–276. DOI: <https://doi.org/10.1016/j.omtn.2021.05.017>, PMID: 34458010
- Shi Y**, Gao X, Hu Q, Li X, Xu J, Lu S, Liu Y, Xu C, Jiang D, Lin J, Xue A, Tan Y, Shen K, Hou Y. 2016. PIK3C2A is a gene-specific target of microRNA-518a-5p in imatinib mesylate-resistant gastrointestinal stromal tumor. *Laboratory Investigation; a Journal of Technical Methods and Pathology* **96**:652–660. DOI: <https://doi.org/10.1038/labinvest.2015.157>, PMID: 26950487
- Shiozawa K**, Shuting J, Yoshioka Y, Ochiya T, Kondo T. 2018. Extracellular vesicle-encapsulated microRNA-761 enhances pazopanib resistance in synovial sarcoma. *Biochemical and Biophysical Research Communications* **495**:1322–1327. DOI: <https://doi.org/10.1016/j.bbrc.2017.11.164>, PMID: 29191657
- Siegel RL**, Miller KD, Jemal A. 2018. Cancer statistics, 2018. *CA* **68**:7–30. DOI: <https://doi.org/10.3322/caac.21442>, PMID: 29313949
- Singh S**, Abu-Zaid A, Jin H, Fang J, Wu Q, Wang T, Feng H, Quarni W, Shao Y, Maxham L, Abdolvahabi A, Yun MK, Vaithiyalingam S, Tan H, Bowling J, Honnell V, Young B, Guo Y, Bajpai R, Pruetz-Miller SM, et al. 2022. Targeting KDM4 for treating PAX3-FOXO1-driven alveolar rhabdomyosarcoma. *Science Translational Medicine* **14**:eabq2096. DOI: <https://doi.org/10.1126/scitranslmed.abq2096>, PMID: 35857643
- Smrke A**, Anderson PM, Gulia A, Gennatas S, Huang PH, Jones RL. 2021. Future directions in the treatment of osteosarcoma. *Cells* **10**:172. DOI: <https://doi.org/10.3390/cells10010172>, PMID: 33467756
- Song B**, Wang Y, Xi Y, Kudo K, Bruheim S, Botchkina GI, Gavin E, Wan Y, Formentini A, Kornmann M, Fodstad O, Ju J. 2009. Mechanism of chemoresistance mediated by miR-140 in human osteosarcoma and colon cancer cells. *Oncogene* **28**:4065–4074. DOI: <https://doi.org/10.1038/onc.2009.274>, PMID: 19734943
- Song L**, Zhou Z, Gan Y, Li P, Xu Y, Zhang Z, Luo F, Xu J, Zhou Q, Dai F. 2019. Long noncoding RNA OIP5-AS1 causes cisplatin resistance in osteosarcoma through inducing the lpaatβ/PI3K/AKT/mTOR signaling pathway by sponging the mir-340-5p. *Journal of Cellular Biochemistry* **120**:9656–9666. DOI: <https://doi.org/10.1002/jcb.28244>, PMID: 30548308
- Sun ZY**, Jian YK, Zhu HY, Li B. 2019. LncRNAPVT1 targets mir-152 to enhance chemoresistance of osteosarcoma to gemcitabine through activating c-MET/PI3K/AKT pathway. *Pathology, Research and Practice* **215**:555–563. DOI: <https://doi.org/10.1016/j.prp.2018.12.013>, PMID: 30661902
- Sun X**, Tian C, Zhang H, Han K, Zhou M, Gan Z, Zhu H, Min D. 2020. Long noncoding RNA OIP5-AS1 mediates resistance to doxorubicin by regulating mir-137-3p/PTN axis in osteosarcoma. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* **128**:110201. DOI: <https://doi.org/10.1016/j.biopha.2020.110201>, PMID: 32460190
- Sun YF**, Wang Y, Li XD, Wang H. 2022. SNHG15, a p53-regulated lncrna, suppresses cisplatin-induced apoptosis and ROS accumulation through the mir-335-3p/ZNF32 axis. *American Journal of Cancer Research* **12**:816–828. PMID: 35261804.
- Tang D**, Kang R, Cheh CW, Livesey KM, Liang X, Schapiro NE, Benschop R, Sparvero LJ, Amoscato AA, Tracey KJ, Zeh HJ, Lotze MT. 2010. Hmgb1 release and redox regulates autophagy and apoptosis in cancer cells. *Oncogene* **29**:5299–5310. DOI: <https://doi.org/10.1038/onc.2010.261>, PMID: 20622903
- Tang X**, Zheng W, Ding M, Guo K, Yuan F, Feng H, Deng B, Sun W, Hou Y, Gao L. 2016. Mir-125B acts as a tumor suppressor in chondrosarcoma cells by the sensitization to doxorubicin through direct targeting the erbb2-regulated glucose metabolism. *Drug Design, Development and Therapy* **10**:571–583. DOI: <https://doi.org/10.2147/DDDT.S90530>, PMID: 26966351
- Tang J**, Duan G, Wang Y, Wang B, Li W, Zhu Z. 2022a. Circular rna_ankib1 accelerates chemo-resistance of osteosarcoma via binding microRNA-26b-5p and modulating enhancer of zeste homolog 2. *Bioengineered* **13**:7351–7366. DOI: <https://doi.org/10.1080/21655979.2022.2037869>, PMID: 35264070
- Tang J**, Zhu Z, Dong S, Wang Y, Wang J, Chen H, Duan G. 2022b. Long non-coding RNA long intergenic non-coding 00641 mediates cell progression with stimulating cisplatin-resistance in osteosarcoma cells via microRNA-320d/myeloid cell leukemia-1 axis. *Bioengineered* **13**:7238–7252. DOI: <https://doi.org/10.1080/21655979.2022.2045090>, PMID: 35266447
- Tawbi HA**, Burgess M, Bolejack V, Van Tine BA, Schuetz SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA, Movva S, Davis LE, Okuno SH, Reed DR, Crowley J, Butterfield LH, Salazar R, Rodriguez-Canales J, Lazar AJ, Wistuba II, et al. 2017. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a

- multicentre, two-cohort, single-arm, open-label, phase 2 trial. *The Lancet. Oncology* **18**:1493–1501. DOI: [https://doi.org/10.1016/S1470-2045\(17\)30624-1](https://doi.org/10.1016/S1470-2045(17)30624-1), PMID: 28988646
- Uçeyler N, Häuser W, Sommer C. 2011. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. *BMC Musculoskeletal Disorders* **12**:245. DOI: <https://doi.org/10.1186/1471-2474-12-245>, PMID: 22034969
- Vanas V, Haigl B, Stockhammer V, Sutterlüty-Fall H. 2016. MicroRNA-21 increases proliferation and cisplatin sensitivity of osteosarcoma-derived cells. *PLOS ONE* **11**:e0161023. DOI: <https://doi.org/10.1371/journal.pone.0161023>, PMID: 27513462
- Vares G, Ahire V, Sunada S, Ho Kim E, Sai S, Chevalier F, Romeo P-H, Yamamoto T, Nakajima T, Saintigny Y. 2020. A multimodal treatment of carbon ions irradiation, mirna-34 and mTOR inhibitor specifically control high-grade chondrosarcoma cancer stem cells. *Radiotherapy and Oncology* **150**:253–261. DOI: <https://doi.org/10.1016/j.radonc.2020.07.034>, PMID: 32717360
- Vicente R, Noël D, Pers YM, Apparailly F, Jorgensen C. 2016. Deregulation and therapeutic potential of microRNAs in arthritic diseases. *Nature Reviews. Rheumatology* **12**:211–220. DOI: <https://doi.org/10.1038/nrrheum.2015.162>, PMID: 26698025
- Wang L, En H, Yang L, Zhang Y, Sun B, Gao J. 2019a. MiR-596 suppresses the expression of survivin and enhances the sensitivity of osteosarcoma cells to the molecular targeting agent anlotinib. *OncoTargets and Therapy* **12**:6825–6838. DOI: <https://doi.org/10.2147/OTT.S215145>, PMID: 31686840
- Wang T, Wang D, Zhang L, Yang P, Wang J, Liu Q, Yan F, Lin F. 2019b. The tgfb β -mir-499a-SHKBP1 pathway induces resistance to EGFR inhibitors in osteosarcoma cancer stem cell-like cells. *Journal of Experimental & Clinical Cancer Research* **38**:226. DOI: <https://doi.org/10.1186/s13046-019-1195-y>, PMID: 31138318
- Wang P, Zhao ZQ, Guo SB, Yang TY, Chang ZQ, Li DH, Zhao W, Wang YX, Sun C, Wang Y, Feng W. 2019c. Roles of microRNA-22 in suppressing proliferation and promoting sensitivity of osteosarcoma cells via metadherin-mediated autophagy. *Orthopaedic Surgery* **11**:285–293. DOI: <https://doi.org/10.1111/os.12442>, PMID: 30932352
- Wang L, Luo Y, Zheng Y, Zheng L, Lin W, Chen Z, Wu S, Chen J, Xie Y. 2020a. Long non-coding RNA LINC00426 contributes to doxorubicin resistance by sponging mir-4319 in osteosarcoma. *Biology Direct* **15**:11. DOI: <https://doi.org/10.1186/s13062-020-00265-4>, PMID: 32620145
- Wang Y, Shang G, Wang W, Qiu E, Pei Y, Zhang X. 2020b. Magnoflorine inhibits the malignant phenotypes and increases cisplatin sensitivity of osteosarcoma cells via regulating mir-410-3p/HMGB1/NF- κ B pathway. *Life Sciences* **256**:117967. DOI: <https://doi.org/10.1016/j.lfs.2020.117967>, PMID: 32553931
- Wang JH, Zeng Z, Sun J, Chen Y, Gao X. 2021. A novel small-molecule antagonist enhances the sensitivity of osteosarcoma to cabozantinib in vitro and in vivo by targeting DNMT-1 correlated with disease severity in human patients. *Pharmacological Research* **173**:105869. DOI: <https://doi.org/10.1016/j.phrs.2021.105869>, PMID: 34481973
- Wang P, Huang Y, Xia X, Han J, Zhang L, Zhao W. 2022a. Pleckstrin homology-like domain family A, member 3, A mir-19a-3p-regulated gene, suppresses tumor growth in osteosarcoma by downregulating the akt pathway. *Bioengineered* **13**:3993–4009. DOI: <https://doi.org/10.1080/21655979.2022.2031404>, PMID: 35112982
- Wang Y, Mo Y, Peng M, Zhang S, Gong Z, Yan Q, Tang Y, He Y, Liao Q, Li X, Wu X, Xiang B, Zhou M, Li Y, Li G, Li X, Zeng Z, Guo C, Xiong W. 2022b. The influence of circular RNAs on autophagy and disease progression. *Autophagy* **18**:240–253. DOI: <https://doi.org/10.1080/15548627.2021.1917131>
- Wang B, Yan L, Shi W, Xie H, Chen R, Shao Y, Liang W. 2022c. CircRNA PVT1 promotes proliferation and chemoresistance of osteosarcoma cells via the mir-24-3p/KLF8 axis. *International Journal of Clinical Oncology* **27**:811–822. DOI: <https://doi.org/10.1007/s10147-022-02122-y>, PMID: 35171359
- Wei R, Cao G, Deng Z, Su J, Cai L. 2016. Mir-140-5P attenuates chemotherapeutic drug-induced cell death by regulating autophagy through inositol 1,4,5-trisphosphate kinase 2 (ip3k2) in human osteosarcoma cells. *Bioscience Reports* **36**:e00392. DOI: <https://doi.org/10.1042/BSR20160238>, PMID: 27582507
- Wibmer C, Leithner A, Zielonke N, Sperl M, Windhager R. 2010. Increasing incidence rates of soft tissue sarcomas? a population-based epidemiologic study and literature review. *Annals of Oncology* **21**:1106–1111. DOI: <https://doi.org/10.1093/annonc/mdp415>, PMID: 19858086
- Wilusz JE, Sharp PA. 2013. Molecular biology: A circuitous route to noncoding RNA. *Science* **340**:440–441. DOI: <https://doi.org/10.1126/science.1238522>, PMID: 23620042
- Wisdom AJ, Mowery YM, Hong CS, Himes JE, Nabet BY, Qin X, Zhang D, Chen L, Fradin H, Patel R, Bassil AM, Muise ES, King DA, Xu ES, Carpenter DJ, Kent CL, Smythe KS, Williams NT, Luo L, Ma Y, et al. 2020. Single cell analysis reveals distinct immune landscapes in transplant and primary sarcomas that determine response or resistance to immunotherapy. *Nature Communications* **11**:6410. DOI: <https://doi.org/10.1038/s41467-020-19917-0>, PMID: 33335088
- Wu H, Tao J, Li X, Zhang T, Zhao L, Wang Y, Zhang L, Xiong J, Zeng Z, Zhan N, Steer CJ, Che L, Dong M, Wang X, Niu J, Li Z, Yan G, Chen X, Song G. 2017. MicroRNA-206 prevents the pathogenesis of hepatocellular carcinoma by modulating expression of met proto-oncogene and cyclin-dependent kinase 6 in mice. *Hepatology* **66**:1952–1967. DOI: <https://doi.org/10.1002/hep.29374>, PMID: 28714063
- Xiao Q, Yang Y, An Q, Qi Y. 2017. MicroRNA-100 suppresses human osteosarcoma cell proliferation and chemo-resistance via ZNRF2. *Oncotarget* **8**:34678–34686. DOI: <https://doi.org/10.18632/oncotarget.16149>, PMID: 28416774
- Xie X, Liu W, Duan Z, Li X, Zhang L, Yang G. 2020. LncRNA NORAD targets mir-410-3p to regulate drug resistance sensitivity of osteosarcoma. *Cellular and Molecular Biology* **66**:143–148. PMID: 32538761.

- Xu M**, Jin H, Xu CX, Bi WZ, Wang Y. 2014. Mir-34C inhibits osteosarcoma metastasis and chemoresistance. *Medical Oncology* **31**:972. DOI: <https://doi.org/10.1007/s12032-014-0972-x>, PMID: 24802328
- Xu Y**, Cheng M, Mi L, Qiu Y, Hao W, Li L. 2018a. Mir-22-3P enhances the chemosensitivity of gastrointestinal stromal tumor cell lines to cisplatin through PTEN/PI3K/akt pathway. *Iranian Journal of Allergy, Asthma, and Immunology* **17**:318–325. DOI: <https://doi.org/10.18502/ijaai.v17i4.91>, PMID: 30537795
- Xu W**, Li Z, Zhu X, Xu R, Xu Y. 2018b. Mir-29 family inhibits resistance to methotrexate and promotes cell apoptosis by targeting COL3A1 and MCL1 in osteosarcoma. *Medical Science Monitor* **24**:8812–8821. DOI: <https://doi.org/10.12659/MSM.911972>, PMID: 30518744
- Yamada H**, Takahashi M, Watanuki M, Watanabe M, Hiraide S, Saijo K, Komine K, Ishioka C. 2021. Lncrna HAR1B has potential to be a predictive marker for pazopanib therapy in patients with sarcoma. *Oncology Letters* **21**:455. DOI: <https://doi.org/10.3892/ol.2021.12716>, PMID: 33907565
- Yan J**, Chen D, Chen X, Sun X, Dong Q, Hu C, Zhou F, Chen W. 2019. Downregulation of lncRNA CCDC26 contributes to imatinib resistance in human gastrointestinal stromal tumors through IGF-1R upregulation. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Medicas e Biologicas* **52**:e8399. DOI: <https://doi.org/10.1590/1414-431x20198399>, PMID: 31166382
- Yang Z**, Wa Q-D, Lu C, Pan W, Lu Z-M, Ao J. 2018. MiR-328-3p enhances the radiosensitivity of osteosarcoma and regulates apoptosis and cell viability via H2AX. *Oncology Reports* **39**:545–553. DOI: <https://doi.org/10.3892/or.2017.6112>, PMID: 29207178
- Yang D**, Xu T, Fan L, Liu K, Li G. 2020. MicroRNA-216B enhances cisplatin-induced apoptosis in osteosarcoma MG63 and saos-2 cells by binding to JMJD2C and regulating the HIF1 α /HES1 signaling axis. *Journal of Experimental & Clinical Cancer Research* **39**:201. DOI: <https://doi.org/10.1186/s13046-020-01670-3>, PMID: 32972441
- Yu WC**, Chen HH, Qu YY, Xu CW, Yang C, Liu Y. 2019. Microrna-221 promotes cisplatin resistance in osteosarcoma cells by targeting PPP2R2A. *Bioscience Reports* **39**:BSR20190198. DOI: <https://doi.org/10.1042/BSR20190198>, PMID: 31221814
- Yu H**, Lin L, Zhang Z, Zhang H, Hu H. 2020. Targeting NF- κ B pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduction and Targeted Therapy* **5**:209. DOI: <https://doi.org/10.1038/s41392-020-00312-6>, PMID: 32958760
- Yuan J**, Chen L, Chen X, Sun W, Zhou X. 2012. Identification of serum microRNA-21 as a biomarker for chemosensitivity and prognosis in human osteosarcoma. *The Journal of International Medical Research* **40**:2090–2097. DOI: <https://doi.org/10.1177/030006051204000606>, PMID: 23321165
- Zajac AE**, Kopec S, Szostakowski B, Spalek MJ, Fiedorowicz M, Bylina E, Filipowicz P, Szumera-Cieckiewicz A, Tysarowski A, Czarnecka AM, Rutkowski P. 2021. Chondrosarcoma-from molecular pathology to novel therapies. *Cancers* **13**:10. DOI: <https://doi.org/10.3390/cancers13102390>, PMID: 34069269
- Zhang Y**, Zhang XO, Chen T, Xiang JF, Yin QF, Xing YH, Zhu S, Yang L, Chen LL. 2013. Circular intronic long noncoding RNAs. *Molecular Cell* **51**:792–806. DOI: <https://doi.org/10.1016/j.molcel.2013.08.017>, PMID: 24035497
- Zhang X**, Guo Q, Chen J, Chen Z. 2015. Quercetin enhances cisplatin sensitivity of human osteosarcoma cells by modulating microrna-217-KRAS axis. *Molecules and Cells* **38**:638–642. DOI: <https://doi.org/10.14348/molcells.2015.0037>, PMID: 26062553
- Zhang CL**, Zhu KP, Shen GQ, Zhu ZS. 2016. A long non-coding RNA contributes to doxorubicin resistance of osteosarcoma. *Tumour Biology* **37**:2737–2748. DOI: <https://doi.org/10.1007/s13277-015-4130-7>, PMID: 26408180
- Zhang Y**, Li D, Feng F, An L, Hui F, Dang D, Zhao Q. 2017a. Progressive and prognosis value of notch receptors and ligands in hepatocellular carcinoma: a systematic review and meta-analysis. *Scientific Reports* **7**:14809. DOI: <https://doi.org/10.1038/s41598-017-14897-6>, PMID: 29093570
- Zhang CL**, Zhu KP, Ma XL. 2017b. Antisense lncrna FOXC2-AS1 promotes doxorubicin resistance in osteosarcoma by increasing the expression of FOXC2. *Cancer Letters* **396**:66–75. DOI: <https://doi.org/10.1016/j.canlet.2017.03.018>, PMID: 28323030
- Zhang H**, Yan J, Lang X, Zhuang Y. 2018. Expression of circ_001569 is upregulated in osteosarcoma and promotes cell proliferation and cisplatin resistance by activating the Wnt/ β -catenin signaling pathway. *Oncology Letters* **16**:5856–5862. DOI: <https://doi.org/10.3892/ol.2018.9410>, PMID: 30344736
- Zhang B**, Liu Y, Zhang J. 2019. Silencing of mir-19a-3p enhances osteosarcoma cells chemosensitivity by elevating the expression of tumor suppressor PTEN. *Oncology Letters* **17**:414–421. DOI: <https://doi.org/10.3892/ol.2018.9592>, PMID: 30655782
- Zhang J**, Rao D, Ma H, Kong D, Xu X, Lu H. 2020a. Lncrna SNHG15 contributes to doxorubicin resistance of osteosarcoma cells through targeting the mir-381-3p/GFRA1 axis. *Open Life Sciences* **15**:871–883. DOI: <https://doi.org/10.1515/biol-2020-0086>, PMID: 33817274
- Zhang Z**, Sun C, Li C, Jiao X, Griffin BB, Dongol S, Wu H, Zhang C, Cao W, Dong R, Yang X, Zhang Q, Kong B. 2020b. Upregulated MELK leads to doxorubicin chemoresistance and M2 macrophage polarization via the mir-34a/JAK2/STAT3 pathway in uterine leiomyosarcoma. *Frontiers in Oncology* **10**:453. DOI: <https://doi.org/10.3389/fonc.2020.00453>, PMID: 32391256
- Zhang Y**, Wang X. 2020c. Targeting the wnt/ β -catenin signaling pathway in cancer. *Journal of Hematology & Oncology* **13**:165. DOI: <https://doi.org/10.1186/s13045-020-00990-3>, PMID: 33276800
- Zhang X**, Xie K, Zhou H, Wu Y, Li C, Liu Y, Liu Z, Xu Q, Liu S, Xiao D, Tao Y. 2020d. Role of non-coding rnas and RNA modifiers in cancer therapy resistance. *Molecular Cancer* **19**:47. DOI: <https://doi.org/10.1186/s12943-020-01171-z>, PMID: 32122355

- Zhang L**, Yang P, Liu Q, Wang J, Yan F, Duan L, Lin F. 2020e. Klf8 promotes cancer stem cell-like phenotypes in osteosarcoma through mir-429-SOX2 signaling. *Neoplasma* **67**:519–527. DOI: https://doi.org/10.4149/neo_2020_190711N624, PMID: 32122144
- Zhang J**, Chen K, Tang Y, Luan X, Zheng X, Lu X, Mao J, Hu L, Zhang S, Zhang X, Chen W. 2021a. Lncrna-hotair activates autophagy and promotes the imatinib resistance of gastrointestinal stromal tumor cells through a mechanism involving the mir-130a/ATG2B pathway. *Cell Death & Disease* **12**:367. DOI: <https://doi.org/10.1038/s41419-021-03650-7>, PMID: 33824300
- Zhang QQ**, Xu SL, Ding C, Ma CC, Yuan TS, Hua CC, Wang XH. 2021b. Lncrna FOXD2-AS1 knockdown inhibits the resistance of human osteosarcoma cells to cisplatin by inhibiting mir-143 expression. *European Review for Medical and Pharmacological Sciences* **25**:678–686. DOI: https://doi.org/10.26355/eurrev_202101_24629, PMID: 33577022
- Zhao G**, Cai C, Yang T, Qiu X, Liao B, Li W, Ji Z, Zhao J, Zhao H, Guo M, Ma Q, Xiao C, Fan Q, Ma B. 2013. MicroRNA-221 induces cell survival and cisplatin resistance through PI3K/Akt pathway in human osteosarcoma. *PLOS ONE* **8**:e53906. DOI: <https://doi.org/10.1371/journal.pone.0053906>, PMID: 23372675
- Zhi W**, Feng Q, Mingzhu Z. 2022. Mir-140 targets Wnt1 to inhibit the proliferation and enhance drug sensitivity in osteosarcoma cells. *Cellular and Molecular Biology* **68**:140–146. DOI: <https://doi.org/10.14715/cmb/2022.68.1.18>
- Zhou Y**, Zhao R, Tseng K, Li K, Lu Z, Liu Y, Han K, Gan Z, Lin S, Hu H, Min D. 2016. Sirolimus induces apoptosis and reverses multidrug resistance in human osteosarcoma cells in vitro via increasing microRNA-34b expression. *Acta Pharmacologica Sinica* **37**:519–529. DOI: <https://doi.org/10.1038/aps.2015.153>, PMID: 26924291
- Zhou B**, Li L, Li Y, Sun H, Zeng C. 2018a. Long noncoding RNA SNHG12 mediates doxorubicin resistance of osteosarcoma via mir-320a/MCL1 axis. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* **106**:850–857. DOI: <https://doi.org/10.1016/j.biopha.2018.07.003>, PMID: 30119255
- Zhou X**, Natino D, Zhai X, Gao Z, He X. 2018b. MicroRNA-22 inhibits the proliferation and migration, and increases the cisplatin sensitivity, of osteosarcoma cells. *Molecular Medicine Reports* **17**:7209–7217. DOI: <https://doi.org/10.3892/mmr.2018.8790>, PMID: 29568877
- Zhou X**, Hao Q, Lu H. 2019. Mutant p53 in cancer therapy—the barrier or the path. *Journal of Molecular Cell Biology* **11**:293–305. DOI: <https://doi.org/10.1093/jmcb/mjy072>, PMID: 30508182
- Zhou Q**, Hu T, Xu Y. 2020. Anticancer potential of TUG1 knockdown in cisplatin-resistant osteosarcoma through inhibition of MET/akt signalling. *Journal of Drug Targeting* **28**:204–211. DOI: <https://doi.org/10.1080/1061186X.2019.1644651>, PMID: 31305159
- Zhu Z**, Wang CP, Zhang YF, Nie L. 2014. MicroRNA-100 resensitizes resistant chondrosarcoma cells to cisplatin through direct targeting of mTOR. *Asian Pacific Journal of Cancer Prevention* **15**:917–923. DOI: <https://doi.org/10.7314/apjcp.2014.15.2.917>, PMID: 24568519
- Zhu KP**, Zhang CL, Shen GQ, Zhu ZS. 2015. Long noncoding RNA expression profiles of the doxorubicin-resistant human osteosarcoma cell line MG63/DXR and its parental cell line MG63 as ascertained by microarray analysis. *International Journal of Clinical and Experimental Pathology* **8**:8754–8773. PMID: 26464619.
- Zhu Z**, Tang J, Wang J, Duan G, Zhou L, Zhou X. 2016. Mir-138 acts as a tumor suppressor by targeting EZH2 and enhances cisplatin-induced apoptosis in osteosarcoma cells. *PLOS ONE* **11**:e0150026. DOI: <https://doi.org/10.1371/journal.pone.0150026>, PMID: 27019355
- Zhu KP**, Zhang CL, Ma XL, Hu JP, Cai T, Zhang L. 2019. Analyzing the interactions of mRNAs and ncRNAs to predict competing endogenous RNA networks in osteosarcoma chemo-resistance. *Molecular Therapy* **27**:518–530. DOI: <https://doi.org/10.1016/j.ymthe.2019.01.001>, PMID: 30692017
- Ziyan W**, Yang L. 2016. MicroRNA-21 regulates the sensitivity to cisplatin in a human osteosarcoma cell line. *Irish Journal of Medical Science* **185**:85–91. DOI: <https://doi.org/10.1007/s11845-014-1225-x>, PMID: 25381586