Cellular Signalling 63 (2019) 109390

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Relevance function of microRNA-708 in the pathogenesis of cancer

Si-nan Sun[a,1], Shuang Hu[b,c,1], Yu-ping Shang[d,1], Liang-yun Li[b,c], Hong Zhou[b,c], Jia-si Chen[b,c], Jun-fa Yang[b,c], Jun Li[b,c], Qiang Huang[a,*], Chuan-pu Shen[e,**], Tao Xu[b,c,**]

[a] The First Affiliation Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, Hefei, Anhui 230001, China
[b] Anhui Province Key Laboratory of Major Autoimmune Diseases, Anhui Institute of Innovative Drugs, School of Pharmacy, Anhui Medical University, Hefei 230032, China
[c] The Key laboratory of Anti-inflammatory and Immune medicines, Ministry of Education, Institute for Liver Diseases of Anhui Medical University, Hefei 230032, China
[d] Anhui Cancer Hospital, Hefei, China
[e] Teaching and Research Department of Traditional Chinese Medicine, Anhui Medical University, Hefei 230032, China

ARTICLE INFO

Keywords:
MicroRNA-708
Cancer
MicroRNA
Clinical application

ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally responsible for regulating > 70% of human genes. MicroRNA-708 (miR-708) is encoded in the intron 1 of the Odd Oz/ten-m homolog 4 (ODZ4) gene. Numerous researches have confirmed that the abnormal expressed miR-708 is involved in the regulation of multiple types of cancer. Notably, the expression level of miR-708 was higher in lung cancer, bladder cancer (BC) and colorectal cancer (CRC) cell lines while lower in hepatocellular carcinoma (HCC), prostate cancer (PC), gastric cancer (GC) and so on. This review provides a current view on the association between miR-708 and several cancers and focuses on the recent studies of miR-708 regulation, discussing its potential as an epigenetic biomarker and therapeutic target for these cancers. In particular, the regulated mechanisms and clinical application of miR-708 in these cancers are also discussed.

1. Introduction

In recent decades, cancer has been one of the most important concerns of the human community, which has been considered a biological heterogeneous disease with distinct genetic abnormalities [1–3]. The GLOBOCAN 2018 estimates presented in this report indicate that there will be 18.1 million new cases of cancer and 9.6 million deaths from cancer in 2018 [4]. Furthermore, some clinical researches exhibited that the crucial step in tumor progression and metastasis is the loss of normal cell polarity and adhesion to achieve mobility and invasiveness [5]. Therefore, cells originated from the tumor and spread far away, which are still the greatest factor in the high mortality rate of cancer patients. However, the lack of useful methods to detect cancer biomarkers or potential targets for cancer treatment is the main reason for the low cure rate of cancer. Thus, it's important for us to understand the process of cancer metastasis and find the key functional domains to treat cancers.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally responsible for regulating > 70% of human genes. They have been increasingly identified as the novel biomarkers or therapeutic targets [6,7]. In addition, miRNAs have been identified as oncogenes or tumor suppressor genes [7]. Among several human microRNAs associated with cancers, miR-708 has been reported to be principally upregulated [8]. Restoration expression of miR-708 in various cancers is one of the leading forces during tumorigenesis by influencing cell proliferation, migration and invasion, suppressing epithelial–mesenchymal transition, enhancing the chemosensitivity and so on [9,10]. For example, the expression level of miR-708 was decreased in hepatocellular carcinoma tissues comparing with the adjacent non-cancerous tissues. Meanwhile, downregulation of miR-708 was associated with aggressive progression of HCC patients, while the enforced expression of miR-708 could retard cell migration and invasive capacity of both HepG2 and SMMC-7721 cells.

In this review, the related miR-708 functional was summarized for the better understanding of the expression patterns and mechanisms of action on cancer and the potential clinical application of miR-708 in various types of cancers. As a result, it can be concluded that miR-708 has significant potential to be used as a diagnostic and prognostic marker for cancers.

* Corresponding author.
** Corresponding authors at: School of Pharmacy, Anhui Medical University, 81 Meishan Road, Hefei, Anhui Province 230032, China.
E-mail addresses: 13505690601@qq.com (Q. Huang), scp1001@126.com (C.-p. Shen), xutao@ahmu.edu.cn (T. Xu).
[1] They contribute equally to this work.

https://doi.org/10.1016/j.cellsig.2019.109390
Received 25 May 2019; Received in revised form 10 August 2019; Accepted 10 August 2019
Available online 13 August 2019

Table 1
The oncogenic or tumor suppressive roles of microRNA-708 in cancers.

microRNA	Cancer type	Cancer cell lines	Expression change	Function in tumorigenesis	Ref. (PMID)
microRNA-708	Prostate carcinoma(PC)	LNCaP, Du145, PC3, VCaP, MDA-PCa-2b	−	Tumor suppressor/Diagnosis and Prognosis marker	22552290 27941876
microRNA-708	Hepatocellular carcinoma (HCC)	HepG2, SMMC-7721, L02	−	Tumor suppressor	26211597 28789462
microRNA-708	Gastric cancer (GC)	gastric tissue, BGC-823, SGC-7901, MGC-803, MKN-45	−	Tumor suppressor/Diagnosis and Prognosis marker	24982912 29444743
microRNA-708	Breast cancer	MDA-MB-231	−	Tumor suppressor	26833707 29575368
microRNA-708	Renal cell carcinoma (RCC)	HK2, A498, Caki2	−	Tumor suppressor	21852381 27092874
microRNA-708	Ovarian cancer (OC)	SKOV-3, TOV-112D, A2780	−	Tumor suppressor	25569036 28685895
microRNA-708	Melanoma	B16 , HEK293	−	Tumor suppressor	29138985 29466930
microRNA-708	Chronic lymphocytic leukemia (CLL)	HEK293T, Primary CLL	−	Tumor suppressor	25704289
microRNA-708	Ewing sarcoma (ES)	SK-ES-1, RD-ES, MRC-5, HEK293T/17, hMSC, EWS502, TC71	−	Tumor suppressor	30470587 22723308
microRNA-708	Osteosarcoma	SaOS-2	−	Tumor suppressor	30783484
microRNA-708	Lung cancer	H520, H2170, H226, H1703, A549, H1299, WI-38	+	Oncogene/Prognosis marker	26678031 28972040
microRNA-708	Bladder cancer (BC)	T24, 5637	+	Oncogene	23568547 22393979
microRNA-708	Colorectal cancer (CRC)	SW480, SW620	+	Oncogene	25202407

"+" indicates an increase in expression, "-" indicates no increase in expression.

2. Overview of cancer

As a major public health problem worldwide, scientists pay attention to cancer research increasingly. Meanwhile, according to estimates from the World Health Organization (WHO), cancer is the second leading cause of death in the world, killing 8.8 million people in 2015. On average, there is about 20% risk of getting a cancer before age 75, and 10% of dying from it [11]. However, approximately 22% of global new diagnosed cancer cases and close to 27% of global cancer deaths occur in China [12,13]. Generally speaking, cancers of breast in female, lung and bronchus, colon and rectum, thyroid, stomach, liver, prostate, cervix, brain, central nervous system (CNS), and pancreas were the top 10 cancer types in urban areas, accounting for 72.81% of all new diagnosed cancers [12]. Simultaneously, tumors refer to a new organism formed by the proliferation of local tissue cells under the action of various tumorigenic factors such as physics, chemistry and viruses. According to the cellular characteristics of the new organism and their harmfulness to the body, tumors are divided into benign tumors and malignant tumors (cancers). On the other hand, cancer cell growth is driven by aberrant signaling and metabolic reprogramming. Cancer cells reprogrammed their metabolism to ensure survival and proliferation in the often nutrient-scarce and stressful microenvironment [14]. Moreover, some oncogenes and tumor suppressor genes play a well-defined role in the selectable agents of tumor proliferation, for example the tumor suppressor gene TP53 [15] and the MET oncogene [16]. Over the past decades, thanks to the advances in early detection, improved treatment and supportive care, the cancer survival rates have increased significantly. However, the means of cancer treatment are still deficient [17]. Unluckily, some traditional therapies like radiotherapy and chemotherapy frequently cause side effects [18,19]. Meanwhile, some biological drugs such as Midostaurin [20], Avelumab [21] and Durvalumab [22] play significant role in some cancers while there are still some unresolved problems. On the other hand, miRNAs have recently emerged as key regulators of carcinogenesis, which can control complex processes like cancer metastization [23]. Among them, the role of miR-708 has been reported to be principally upregulated while further studies are still necessary to be investigated [8].

3. Overview of miR-708

MiR-708 is encoded in the intron 1 of the ODZ4 gene which is regulated by CCAAT enhancer-binding homologous protein (CHOP) in vertebrates [24]. In addition, miR-708 could be divided into two types: miR-708-3p and miR-708-5p. Meanwhile, it could act as a gatekeeper of quiescence by modulating muscle stem cell. In recent years, it was demonstrated that miR-708 could regulate quiescence and self-renewal by antagonizing cell migration through targeting the transcripts of the focal-adhesion associated protein Tensin3 [25]. It is generally known that immunoevasion is a hallmark of cancer progression. Immune checkpoint blockade has emerged as a promising strategy for cancer treatment [26,27]. Interestingly, it was confirmed that miR-708 directly targeted CD47 (a transmembrane protein that inhibits phagocytosis in T cell acute lymphoblastic leukemia) through binding to 3′-UTR and is inversely correlated with CD47 expression. What's more, further research confirmed that miR-708-5p could promote fibroblast-like synoviocytes' cell apoptosis and ameliorate rheumatoid arthritis by inhibiting Wnt3a/β-catenin signaling pathway [3,28]. On the other hand, miR-708-3p was more significantly decreased in invasive breast cancer cell lines. Simultaneously, miR-708-3p could inhibit breast cancer cell epithelial-to-mesenchymal transition (EMT) by targeting EMT activators, including ZEB1, CDH2 and vimentin [10]. Of note, miR-708 has been demonstrated to have profound roles in suppressing oncogenesis in different types of tumors [28]. Functional studies showed that restoration of miR-708 expression in the T-ALL cell line was sufficient to promote phagocytosis by macrophages in the absence or presence of the anti-CD47 antibody to eradicate T-ALL cells, and inhibited tumor

Table 2
The targets of microRNA-708 in cancers.

microRNA	Cancer type	Target	Ref. (PMID)
microRNA-708	Prostate carcinoma(PC)	Karyopherin α4 (KPNA4)	27941876
microRNA-708	Hepatocellular carcinoma (HCC)	SMAD3	28789462
microRNA-708	Gastric cancer (GC)	Notch1	24982912
microRNA-708	Breast cancer	Lysine-specific histone demethylase 1 (LSD1), ZEB1, CDH2 and vimentin	26833707 29575368
microRNA-708	Renal cell carcinoma (RCC)	Cellular FLICE-like inhibitory protein (c-FLIP), ZEB2, BMI1	21852381 27092874
microRNA-708	Ovarian cancer (OC)	Caspase-3	28685895
microRNA-708	Melanoma	Lymphoid enhancer-binding factor-1 (LEF1)	28500952
microRNA-708	Lung cancer	DNA methyltransferase 3A (DNMT3A)	28972040
microRNA-708	Bladder cancer (BC)	Caspase-2	23568547
microRNA-708	Colorectal cancer (CRC)	Cyclin-dependent kinase inhibitor 2B (CDKN2B)	25202407

engraftment in vivo [29]. Thus, miR-708 may become a favorable option for treating cancer by inhibiting cancer metastasis and overcoming the chemoresistance.

4. The regulatory role of miR-708 in various types of cancer

Numerous studies have shown that miRNA play an important role in the progression of cancer [30]. What's more, Wu et al. found that the expression of miR-708-5p was substantially reduced in metastatic lung cancer samples and cancer cell lines via regulating the PI3K/AKT signaling pathway [7]. Simultaneously, miR-708 could also target Notch1 to inhibit cell proliferation and invasion in gastric cancer [9]. Recently, it was proved that miR-708 has been reported to be aberrantly expressed in several types of cancer and contributes to carcinogenesis and progression, with suppressing cancer cell invasion, metastasis and so on [31]. In this review, we selected 12 types of cancer and summarized the effects of miR-708 in different cancers, suggesting that miR-708 played an important role in cancer progression (as shown in Tables 1, 2). In addition, the clinical potential effect of miR-708 in cancer therapy and prognosis was also summarized.

4.1. MiR-708 as a tumor suppressor

4.1.1. Prostate cancer

PC is the most common cancer in men and it's the second leading cause of cancer-associated mortality in USA. In 2012, the incidence of PC in Europe was estimated to be 417,000 and the mortality was 92,000 [32,33]. Currently, the treatment for PC includes surgery, androgen deprivation therapy, chemotherapy, and radiation [34]. However, the related therapeutic methods usually lead to severe side effects and drug resistance, even progress into castration resistant prostate cancer (CRPC) in PC patients [35]. Therefore, new therapeutic agents are urgently needed to be found. Of note, tumor recurrence in PC has been attributed to the presence of CD44-expressing tumor-initiating cells. Interestingly, the relevant investigation reported that miR-708 is a key negative regulator of this $CD44^+$ subpopulation of PC cells, with significant implications for diagnosis and prognosis of this disease. Interestingly, reconstitution of miR-708 led to decrease tumorigenicity in PC cell lines by regulating the expression of CD44 as well as serine/threonine kinase AKT2 in vitro [36]. Furthermore, karyopherin α4 (KPNA4) mediates the cytoplasm-to-nucleus translocation of transcription factors, including nuclear factor-kappa-B (NF-κB). It could also alter tumor microenvironment in terms of macrophage polarization and osteoclastogenesis by modulating tumor necrosis factor (TNF)-α and -β. On the other hand, KPNA4 silencing could reduce cell migration and inhibit the PC invasion and distant metastasis in mouse. Meanwhile, a dual-luciferase reporter confirmed that KPNA4 was a direct target of miR-708 [37]. Therefore, miR-708 may become a beneficial agent to induce PC cells apoptosis and miR-708-KPNA4-TNF axes might play a significant role in PC metastasis.

4.1.2. Hepatocellular carcinoma

HCC is the one of most common cancers accounting for 90% of these cases and is the third most common cause of cancer-related death [38]. Of note, HCC is considered one of the most lethal and prevalent neoplasias worldwide, with a poor prognosis and survival rate [39,40]. Unfortunately, there is a lack of ideal drugs for HCC treatment, due to the multidrug resistance and hepatotoxicity of systemic chemotherapy drugs [41]. However, Li et al. confirmed that miR-708 was significantly downregulated about 88% in HCC tissues comparing with the adjacent non-cancerous tissues. Furthermore, downregulation of miR-708 was associated with aggressive progression of HCC patients, while the enforced expression of miR-708 could retard cell migration and invasive capacity of both HepG2 and SMMC-7721 cells compared with miR-NC-transfected control cells [24]. Moreover, Smad was an oncogene in numerous types of cancer, directly. Meanwhile, Wu et al. exhibited that HCC cell proliferation was related to the SMAD3 expression [42]. Amazingly, bioinformatic analysis was performed that miR-708 significantly decreased luciferase activity in the wild-type Smad3 3′-UTR-transfected HepG2 and SMMC-7721 cells comparing with the cells transfected with the mutated Smad3 3′-UTR [43]. Further study performed that the Smad3 protein was significantly down-regulated in the HepG2 and SMMC-7721 cells. Meanwhile, the HCC cells proliferation, migration and invasion were alleviated. Thus, miR-708 may be a novel target for future HCC therapy via retarding cell migration and invasive capacity.

4.1.3. Gastric cancer

GC or stomach cancer (SC), the fourth leading cancer worldwide, is a biologically heterogeneous disease, leading to > 720,000 deaths annually. It is the second major contributor to mortality caused by cancer [44,45]. Furthermore, although progress has been made in elucidation of pathogenesis and treatment strategies to improve the high morbidity and mortality of GC patients, due to the lack of effective early detection and primary, most patients once diagnosed have been at the late-stage due to the lack of effective early detection [45]. Meanwhile, GC has multifactorial etiology and molecular complexity, which challenges the discovery of molecular markers [46]. What's more, it was confirmed that miR-708 was down-regulated in GC cell lines (BGC-823, MKN-45, SGC-7901, and MGC-803 cell lines). Meanwhile, downregulation of miR-708 expression was closely related to lymphatic metastasis and invasion depth. Additionally, bioinformatics analysis predicted that Notch1 might be as a candidate target of miR-708 and the results of luciferase reporter assays confirmed that miR-708 directly targeted the 3′-UTR of Notch1. Notably, Notch1 played a notable role in GC as an oncogene, which participated in the onset and progression of GC by regulating proliferation, apoptosis, colony formation, and metastasis, which confirmed as an independent prognostic factor of patients with GC. Interestingly, further study found that restored Notch1 expression rescued the inhibitory effects on GC cell proliferation and invasion induced by miR-708 overexpression [9,44]. In summary, miR-708 may be investigated as a novel target for GC treatment by regulating

proliferation, apoptosis, invasion and metastasis.

4.1.4. Breast cancer

Breast cancer was the second-leading cause of mortality in female and the most frequently diagnosed cancer in the USA. Meanwhile, breast cancer was estimated 252,710 new cases and 40,610 expected breast cancer deaths every year [47]. Up to now, the majority of breast cancer morbidity and mortality is due to incurable metastatic disease that is highly resistant to conventional therapies [48]. Thus, it is essential to further elucidate the molecular mechanisms of breast cancer metastasis, and develop novel therapeutic approaches to reduce breast cancer mortality. Interestingly, Ma et al. identified that miR-708 had a negative correlation with cell proliferation by using CCK8 assay. Moreover, overexpression of miR-708 decreased MDA-MB-231 cells invasion, whereas inhibition of miR-708 promoted MDA-MB-231 cells invasion. On the other hand, Lysine-specific histone demethylase 1 (LSD1) is a kind of histone demethylase which specifically demethylated mono- and dimethylated lysine 4 and lysine 9 of histone H3 [49]. which is highly expressed in various cancers, playing a pivotal role in different cancer-related processes. Meanwhile, LSD1 plays pivotal role in breast carcinoma and suggesting a possible molecular mechanism to some extent [50,51]. At the same time, the related study confirmed that miR-708 specifically regulated LSD1 to inhibit proliferation and invasion in breast cancer [49]. Furthermore, miR-708-3p was more significantly decreased in invasive breast cancer cell lines. Simultaneously, overexpression of miR-708-3p dramatically could inhibit breast cancer cells metastasis and enhance the sensitivity of breast cancer cells to chemotherapy both in vitro and in vivo. Of note, EMT, a cellular program that operates in the context of embryogenesis, plays an important role in breast cancer cell metastasis [52]. Lee et al. found that miR-708-3p could inhibit breast cancer cell EMT by directly targeting EMT activators [10]. Hence, it suggested the potential application of miR-708/LSD1 axis and restoration of miR-708-3p may be a novel strategy for inhibiting breast cancer metastasis and overcoming the chemoresistance of breast cancer cells.

4.1.5. Renal cell carcinoma

Renal cell carcinoma (RCC) is a malignant tumor of the urinary system, which originates from renal tubular epithelial cells [53]. There is a continued increase in the incidence of kidney cancer with approximately 65,340 new cases in the USA and 14,970 deaths each year. Meanwhile, RCC is the second leading urogenital malignancy in China, accounting for 2%–3% of all adult cancers [54]. In the early stage of RCC, surgery is a good choice for the treatment of RCC. However, in the late stage of RCC, metastasis, and drug resistance of RCC are the main problems in RCC treatment [55]. At the same time, RCC is not sensitive to radiotherapy, chemotherapy or immunotherapy, and their effects are limited and poor [53]. This is the reason why researchers need to find new molecular targets to develop specific agents for targeted therapy with fewer adverse effects. Surprisingly, miR-708 re-expression led to marked morphologic changes and suggested a profound increase in apoptotic cells. Thus, the tumorigenicity of RCC was suppressed in vitro [56,57]. Moreover, it was observed that miR-708 regulated tumorigenicity by leading to the induction of TNF-related apoptosis-inducing ligand to induce apoptosis. Meanwhile, miR-708 overexpression decreased protein expression level of surviving (surviving was a small inhibitor of apoptosis protein that is differentially expressed in cancer) and played important roles in RCC progression and metastasis. It suggested that the proapoptotic role of miR-708 may be mediated primarily via regulating surviving expression [58]. What's more, miR-708 could target the E-cadherin regulator ZEB2 (a transcriptional repressor that regulates the expression of E-cadherin and EMT) and the polycomb repressor, BMI1. Thus, these data showed the antitumorigenic role of miR-708 in RCC in vitro. Further study also estimated that intratumorally delivery of miR-708 leads to regression of tumors in a RCC xenograft model [58]. On the other hand, the dysregulation of the anti-apoptotic protein, cellular FLICE-like inhibitory protein (c-FLIP) has been associated with tumorigenesis and chemoresistance in various human cancers [59]. Interestingly, miR-708 expression was suppressed whereas c-FLIP$_L$ was upregulated in RCC. Luciferase reporter assays demonstrated that miRNA-708 negatively regulated c-FLIP$_L$ expression by binding to the 3′UTR of c-FLIP$_L$. Thus, the accumulation of sub-G1 populations, cleavage of procaspase-3 and PARP were increased and the sensitivity of renal cancer cells to anti-cancer drugs was improved [60]. In conclusion, these data confirmed the main anti-cancer effect of miR-708, which may provide an attractive new target for the prognosis and therapeutic intervention of RCC.

4.1.6. Ovarian cancer

Ovarian cancer (OC), the second most common female reproductive malignant tumor (240,000 new cases annually), is the leading cause of death in gynecological malignancy (over 150,000 new deaths annually) worldwide [61,62]. There are only a modest improvement in OC patient prognosis over the last several decades [63]. In 80% of patients with advanced OC, the disease recurs despite optimal surgical cytoreduction and adjuvant systemic platinum-based chemotherapy [64]. Recent study estimated that miR-708 expression was downregulated in cisplatin-resistant OC cells relative to the parental controls, suggesting its potential implication in drug resistance [61,65]. Amusingly, overexpression of miR-708 increased the sensitivity of cisplatin-resistant SKOV3/DDP and A2780/DDP cells to cisplatin-induced toxicity, reducing the 50% inhibitory concentration (IC50). In addition, it has been documented that cisplatin causes Caspase-3-dependent apoptosis in OC cells [65]. Interestingly, overexpression of miR-708 significantly facilitated the cleavage of Caspase-3 in parental and cisplatin-resistant OC cells after cisplatin treatment [66]. Therefore, miR-708-mediated chemosensitization is likely associated with induction of Caspase-3-dependent apoptotic cascade [65]. Thus, these results confirmed the therapeutic potential of miR-708 in improving cisplatin toxicity against OC.

4.1.7. Melanoma

Melanoma is one of the most aggressive forms of skin cancers, which is characterized by a marked metastatic potential that represents the major cause of death in patients [67]. Accounting for about 5% of all skin cancer cases, melanoma is the most dangerous form of skin malignancy and causes about 90% of skin cancer mortalities [68]. Up to now, radiotherapy is the main treatment for melanoma. The successful control of local lesions is as high as 80% [69]. Despite successful control of localized disease, however, patients frequently develop metastases, including in the brain, which result in overall treatment failure. Interestingly, the related study showed that the expression of miR-708 was decreased in melanoma cells (B16 and A375). In addition, lymphoid enhancer-binding factor-1 (LEF1), as the one of 48-kD nuclear proteins, is a very significant member of the Wnt/β-catenin in embryonic stem cells and often are expressed in the T and pre-B cells [70]. Song et al. found that miR-708 inhibited the proliferation, invasion, migration, and EMT in B16 and A375 cells. EMT involved melanoma cells by targeting LEF1 through the Wnt signaling pathway [71]. Simultaneously, the over-introduction of miR-708 had elevated expressions of Bax, caspase3, and E-cadherin, while also enhanced B16 and A375 cells apoptosis [72]. In conclusion, miR-708 has a potential therapeutic effect on melanoma via the suppression of Wnt/β-catenin signaling pathway.

4.1.8. Chronic lymphoblastic leukemia

Chronic lymphocytic leukemia (CLL) is a clonal disorder of mature B cells with stereotypic BCRs characterized by the expression of CD19, CD23, and CD5. Of note, the 5-year survival rate for CLL patients is 79.2%, with about 4.5 cases per 100,000 individuals reported annually [73]. Of note, the development of CLL is the consequence of malignant cell transformation, microenvironment-induced proliferation, and

evasion of immune surveillance [74]. Meanwhile, related study confirmed that the NF-κB signaling pathway is constitutively activated while miR-708 expression is reduced in CLL patients [75,76]. Interestingly, further study reported that miR-708 strongly repressed NF-κB signaling pathway by targeting inhibitor of kappa light polypeptide gene enhancer in B cells, kinase-β/IKBKB (IKKβ). IKKβ is a key kinase facilitating NF-κB signaling [76]. However, the ultimate efficacy of CLL remains undetected, more investigations are needed to be investigated [77].

4.1.9. Ewing's sarcoma

Ewing sarcoma (ES), the second most common malignant bone tumor in children, adolescents and young adults, which results from pathognomonic balanced t(11;22)(q24;q12) chromosomal translocations between EWSR1 and one of several genes in the ETS family of transcription factors [77–79]. Despite advances in its treatment over the past few decades, the survival rate of its patients is unsatisfactory, suggesting an urgent need for more effective treatment centered on the molecular basis of ES [78]. ES was characterized by the presence of the nonphysiologic fusion protein transcription factor, EWS/FLI1. EWS/FLI1 was originated from a chromosomal translocation that brings together the EWS gene on chromosome 22, with the FLI1 gene on chromosome 11 [80]. At the same time, EYA3 is highly expressed in ES tumor samples and cell lines compared with mesenchymal stem cells, the presumed cell-of-origin of ES. What's more, it is regulated by the EWS/FLI1 fusion protein transcription factor. Interestingly, EWS/FLI1 regulates EYA3 in ES via modulation of miRNA-708, resulting in increased cell survival and chemoresistance [81,82]. However, the expression level of miR-708 was down-regulated in EWS samples and previously described as chemical sensitizers, this miRNA-708 does not affect tumor growth but instead it strongly stimulates tumor invasion which is not appropriate for future therapeutic intervention.

4.1.10. Osteosarcoma

Osteosarcoma is the most frequent primary solid malignancy of bone in the young adolescent [83]. Following the implementation of chemotherapy in the 1970s, the 5-year overall survival rate of osteosarcoma increased dramatically to 60%–70%. Since then, however, no further significant improvements in the survival rate have been achieved, mainly because of chemoresistance [84]. In spite of existing achievements in treatment approaches, overall survival among patients with OS remains unsatisfactory. Hence, better illustration on the molecular mechanism behind osteosarcoma is of necessity [85]. Interestingly, Sui et al. confirmed that the expression level of miR-708-5p was significantly downregulated in osteosarcoma tissues and SaOS-2 cells. The results indicated that miR-708-5p was significantly downregulated in osteosarcoma tissues and cells. Meanwhile, the overexpression of miR-708-5p significantly inhibited cell viability, invasion and migration and induced apoptosis of SaOS-2 cells [86]. Moreover, the related results indicated that miR-708-5p directly targeted the 3′-untranslated region of up-regulator of cell proliferation (URGCP) and negatively regulated its expression in SaOS-2 cell [86] Taken together, the current study suggested that miR-708-5p may inhibit the growth and invasion of osteosarcoma cells via regulating the URGCP/NF- κB signaling pathway. Further research on these molecules in osteosarcoma may provide novel insights into the target therapy for this disease.

4.2. MiR-708-5p as an oncogenic miRNA

4.2.1. Lung cancer

Lung cancer is the leading cause of cancer death worldwide and 80% patients have non-small cell lung cancer (NSCLC) including lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), lung large-cell carcinoma, and lung adenosquamous carcinoma. Simultaneously, NSCLC is often diagnosed at later stages with around 15% of 5-year survival rates [87–89]. Therefore, the NSCLC has become one of the most devastating diseases to human beings due to its high morbidity, high mortality and low diagnostic rate, so effective early diagnosis of NSCLC is an urgent matter [90]. However, the traditional therapy is mainly consisted of chemotherapy, radiotherapy, surgical resection and best supportive care. In recent years, the therapeutic strategies for NSCLC have been enriched with small molecular targeted therapy and immunotherapy [91]. Among them, miR-708-5p stood out as a highly expressed miRNA in non-metastatic lung cancer cell lines when compared with highly metastatic cells. The result of qRT-PCR analysis showed that expression of miR-708-5p was markedly reduced in the high metastatic group when compared to the low metastatic group [7]. Furthermore, miR-708-5p, as an anti-metastatic miRNA and a direct negative regulator, exhibited the effects on suppressing not only total p21, but also the cytoplasmic localization of p21, which in turn elevated apoptosis and weaken actin rearrangement, leading to decrease cell motility [6,7]. Importantly, in the era of targeted therapy, it was concluded that p21 was indeed a direct functional mediator of miR-708-5p. Simultaneously, miR-708-5p impaired lung cancer cell migration and promoted cancer cell apoptosis by inhibiting the cytoplasmic localization of p21 [7]. On the other hand, DNA methyltransferase 3A (DNMT3A) showed the vital activity in cancers by inhibiting cancer cell proliferation [92] or being a prognostic agent [93]. Furthermore, DNMT3A as a direct target of miR-708-5p, had been identified to carry out de novo methylation during the processes of development, stem cell regulation and progression of several diseases in mammals. However, miR-708-5p directly suppressed the translation of DNMT3A, which resulted in a substantial reduction of global DNA methylation and the up-regulated expression of tumor suppressor CDH1. The up-regulation of CDH1 decreased the activity of Wnt/β-catenin signaling and then impaired the stemness charactertics of NSCLC cells [94]. Thus, if chemotherapeutic treatment of cancer cells could be integrated with the use of a miR-708-5p mimic, the tumors may then become more susceptible to the drug targeting and apoptosis, improving the efficiency of chemotherapy.

4.2.2. Bladder carcinoma

Bladder carcinoma is one of the most lethal malignancies worldwide. In 2012 alone, an estimated 430,000 new cases and 165,000 deaths occurred worldwide, with 75% of the burden in men [95]. According to the epidemiological studies, a range of genetic, anatomical, hormonal, social, and environmental factors could help trigger the disease [96,97]. A better understanding of the relevant factors of disease incidence will provide insights into the formulation of more effective treatment strategies. Recently, differential miRNA expression profiles in bladder carcinoma identified miR-708 up-regulation among the most common alterations [97]. What's more, Song et al. reported that miR-708 silencing could promote the T24 and 5637 cells to apoptosis and inhibit the bladder tumor growth in vivo. Meanwhile, Caspase-2 was an enzyme that played a central role in the execution-phase of cell apoptosis. Interestingly, the expression level of miR-708 is observed to be negatively associated with the mRNA level of Caspase-2 in bladder carcinoma tissue. Meanwhile, Caspase-2 was proved to be one of direct targets of miR-708 by using the Targetscan bioinformatics tool [98]. Thus, it's showed that Caspase-2 was involved in the miR-708 regulated cell apoptosis. In conclusion, miR-708 expression profile might be used as diagnostic biomarker of bladder carcinoma.

4.2.3. Colorectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide, affecting approximately 112,000 new patients every year [99,100]. Despite improvements in surgical and adjuvant chemotherapy treatment, 5-years survival rates from CRC still remain unsatisfactory [100]. This is the reason why we need to find a more effective treatment for cancer. Coincidently, miR-708 was found to be highly expressed in five CRC tissue samples. Simultaneously, the inhibition of miR-708 inhibited CRC cells proliferation and invasion,

however, promoted cells apoptosis in vitro [101]. Moreover, cyclin-dependent kinase inhibitor 2B (CDKN2B) is associated with various cancers [102]. Subsequently, Lei et al. confirmed that miR-708 directly targeted CDKN2B by binding to the 3′UTR of CDKN2B that inhibited the expression level of CDKN2B. In addition, the CDKN2B protein expression level was significantly reduced when high miR-708 expression was detected in the CRC tissue samples [101]. Thus, miR-708 plays the carcinogenic role in the development of CRC, and inhibition of miR-708 can be used as a therapeutic strategy for patients with CRC.

5. The potential clinical application of miR-708 in various types of cancers

Cancer is hard to be detected in early stages, thus, it's easy to lose the best chance for curative surgery and result in the poor survival rates. Obvious cancer biomarkers to monitor molecular differences in cancers for the earliest diagnosis is indispensable, which may be helpful in the selection of the best possible treatment. On the other hand, the current research has deeply explored the viability of using miRNA expression profiles for predicting cancer or discriminating between cancer subtypes. However, owing to the uncertain molecular biological functions, miRNA biomarkers cannot accurately predict cancer progression. miR-708 may be critical players and regulators in carcinogenesis and progression, and serve as potential biomarkers for various cancers [33]. The ideal and convenient biomarkers should possess several typical and important characteristics. For example, it should be detected easily in body fluids such as blood, urine and semen, as well as its expression was significantly different between cancer and normal tissues. More importantly, its abnormal expression was significantly associated with patients' clinical features such as prostate-specific antigen (PSA), Gleason score and TNM status. Furthermore, the related research reported that down-regulated miR-708 expression was significantly associated with lymphatic metastasis, invasive depth and TNM stage [9]. Therefore, this section was to sum up most of reported miR-708 which could be used as diagnostic and prognostic biomarkers for various cancers.

Leidinger et al. have reported that the expression of miR-708 in human PC tissues was closely associated with high PSA levels, Gleason scores, and tumor volume. Simultaneously, it was identified that miR-708 were significantly deregulated in the comparison of PC versus benign prostatic hyperplasia (BPH) patients [33]. The decreased miR-708 expression was observed in 63% of cases of low Gleason score,74% of cases of Gleason score, and 90% of cases of higher Gleason score. Importantly, miR-708 was specifically attenuated in 18 of 22 cases (82%) of PSA failure within this cohort of samples, which suggested that downregulation of miR-708 was associated with biochemical recurrence [33,103]. Moreover, receiver operating characteristic (ROC) analyses showed that miR-708 expression can be a single significant parameter to discriminate between normal and tumor tissues with an area under the ROC curve (AUC) of 0.937 (95% confidence interval (CI), 0.901–0.963; $P < .0001$). Similarly, according to the survival analysis of PC patients stratified by miR-708 level, the survival rate of patients with low expression of miR-708 was significantly reduced. The HR between the cases with low or high miR-708 expression was 6 with a 95% CI from 2.2 to 16.4 and with an associated P value of 0.0223 [36]. It suggested that miR-708 had significant potential to be used as a diagnostic and prognostic marker for PC.

Squamous cell carcinoma (SCC) is a common form of lung cancer. Xing et al. identified that miR-708 was upregulated in lung squamous cell carcinoma (LSCC) sample comparing with normal sample [104]. Meanwhile, ROC analyses were confirmed that the AUC value was 0.756. When the cutoff value = 4.48, the diagnostic sensitivity (65%) and specificity (75%) reached their peak values ($P < .001$). However, miR-205 and miR-210 also played an important role in LSCC, the combination of the three miRNAs produced 0.866 AUC, being considerably higher than 0.623–0.789 AUC values of each individual gene in distinguishing cancer patients from normal subjects (all $P < .05$) [105,106]. Thus, these results suggested that the expression of these three miRNAs were complementary to play a crucial role in LSCC and served as a new potential biomarker for clinical prognosis evaluation.

Importantly, researchers got GC specific miRNA-mRNA subnetwork and 17 candidate GC miRNAs for biomarkers with regulatory roles by using POMA. The study confirmed that the indispensable role of miR-708 in GC. Another study also reported that miR-708 expression was down-regulated in GC tissue and cell lines and the down-regulated miR-708 expression was significantly associated with lymphatic metastasis ($P = .040$), invasive depth ($P = .019$) and TNM stage ($P = .038$) [9,44]. What's more, the ROC curve was constructed for differentiating GC patients from controls. Compared to matched adjacent nontumorous tissues, the AUC was up to 0.835, the accuracy was 0.700 and the sensitivity and specificity were 0.888 and 0.378. At the same time, the miR-211 and let-7b also expressed the potential candidate biomarkers for human GC and the values of AUC, sensitivity and specificity showed the high levels [44]. Therefore, the three miRNAs could be potential novel biomarkers for GC diagnosis and treatment while the candidates predicted herein need further wet-lab validation.

Delayed diagnosis, recurrence, and metastasis are the biggest obstacles to the treatment of cancers. Therefore, searching for the ideal biomarkers of cancers is essential for improving the early diagnostic rate. The above findings indicated that miR-708 might be used as a potential marker for the PC, LSCC and GC diagnosis. The related data are shown in Table 3. However, the precise molecular mechanisms by which miR-708 functions in various cancers remain obscure. Further exploratory and validation research is needed to elucidate the functional role of miR-708 in cancers, especially in clinical applications.

6. The regulatory mechanism of miR-708 in various types of cancer

It is well known that the reasons why cancers are hard to cure due to their complex tumorigenesis and metastasis. Gradually, it was found that miR-708 might effective biomarkers for determining cancers occurrence and metastasis through direct or indirect regulation. Here, we summary the related regulatory mechanisms involved in the occurrence and development of cancers.

Firstly, miR-708 directly affects the progression of various cancers through some signaling pathways (as shown in Fig. 1). Of note, Wnt/β-catenin signaling pathway, which is the key regulator for the progression of HCC, plays a critical role in the development and stemness of cancer cells [107]. In addition, lymphoid enhancer-binding factor-1 (LEF1) is one nuclear protein that is often expressed in the T and pre-B cells and is also a very significant member of the Wnt/β-catenin signaling pathway in embryonic stem cells [70]. Song et al. found that miR-708 played a role in the proliferation, invasion, migration and EMT

Table 3
Potential clinical application of microRNA-708 as diagnostic marker in cancers.

microRNA	Cancer type	Cutoff value	AUC	Sensitivity	Specificity	Ref. (PMID)
microRNA-708	Prostate carcinoma(PC)		0.937			22,552,290
microRNA-708	Lung cancer	4.48	0.756	0.65	0.75	20526284
microRNA-708	Gastric cancer (GC)		0.835	0.888	0.378	24982912

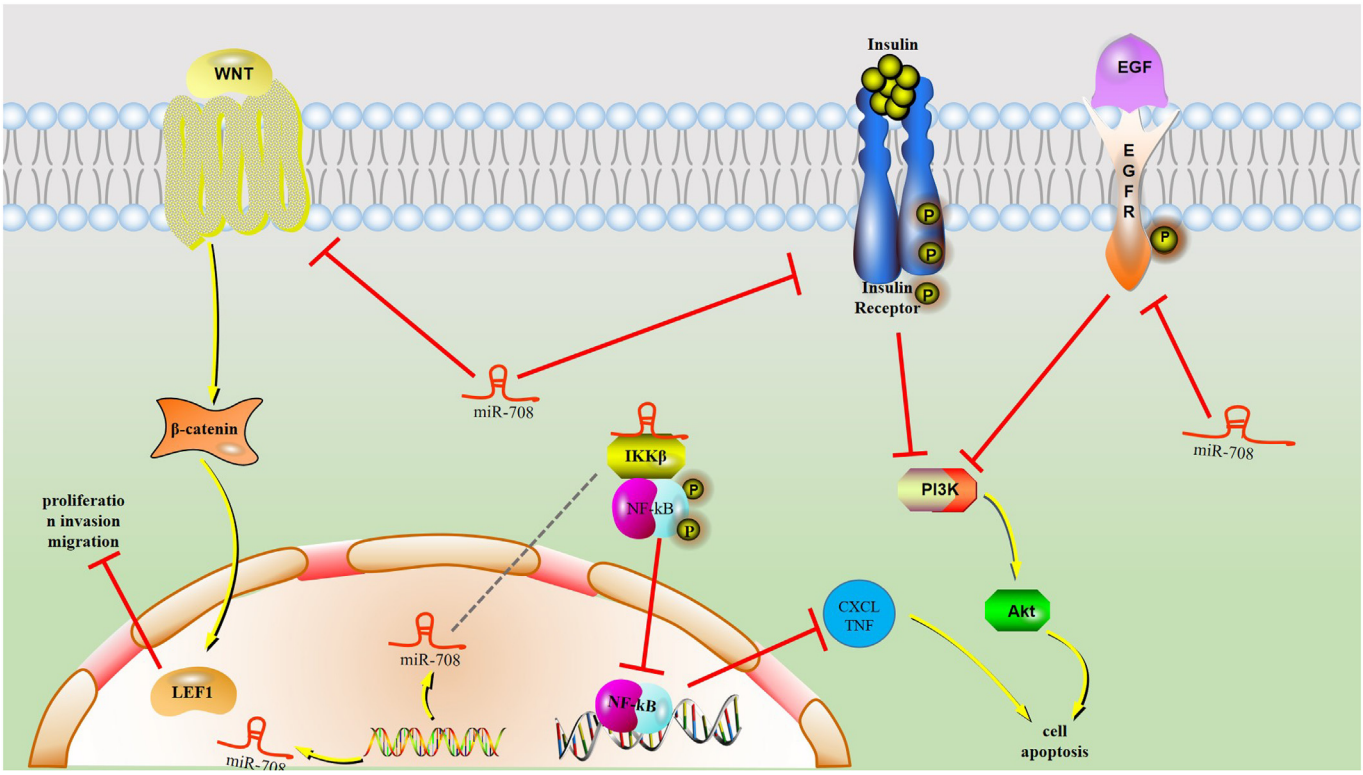

Fig. 1. Regulatory function of miR-708 in various cancers directly. Firstly, miR-708 played a role in the proliferation, invasion, migration and EMT of melanoma cells by targeting LEF1 through the Wnt/β-catenin signaling pathway. Secondly, miR-708-5p inhibited the PI3K/AKT signaling pathway and stem cell-like characteristics of lung cancer cells through down-regulating multiple receptor tyrosine kinases, such as the EGF receptor family genes and insulin receptor family genes. Simultaneously, miR-708 downregulated the expression of insulin like growth factor 2 mRNA binding protein 1 (IGF2BP1) and suppressed AKT phosphorylation. In addition, miR-708 strongly repressed NF-κB signaling pathway by targeting inhibitor of kappa light polypeptide gene enhancer (kinase-β/IKBKB (IKKβ)) in B cells, which is a key kinase facilitating NF-κB signaling, and contributes to inhibit CLL.

of melanoma cells by targeting LEF1 through the Wnt/β-catenin signaling pathway [71,72]. Meanwhile, miR-708-5p inhibited the CSC characteristics of NSCLC cells in vitro. The upregulation of CDH1 decreased the activity of Wnt/β-catenin signaling pathway and then impaired the stemness characteristics of NSCLC cells [94]. Furthermore, AKT, the key transcriptional factors in Wnt/β-catenin signaling pathway, is involved in progression and development with tumor. PI3K/AKT is essential in regulating cell growth, motility, apoptosis and metastasis in cancer process [108]. Importantly, in the era of targeted therapy, a prominent and well-defined role of the PI3K/AKT signaling pathway in modulating cancer cell growth and survival has motivated development of PI3K/AKT signaling pathway inhibitors as a promising and effective therapy for malignant solid cancers. The RNA-seq data showed that miR-708-5p inhibited the PI3K/AKT signaling pathway and stem cell-like characteristics of lung cancer cells through down-regulating multiple receptor tyrosine kinases, such as the EGF receptor family genes and insulin receptor family genes [7]. Similarly, miR-708 downregulated the expression of insulin like growth factor 2 mRNA binding protein 1 (IGF2BP1) and suppressed AKT phosphorylation. Furthermore, IGF2BP1 silencing markedly blocked the phosphorylation of AKT. Overexpression of IGF2BP1 restored cisplatin resistance and AKT phosphorylation in miR-708-overexpressing OC cells. Thus, miR-708 could increase the susceptibility of OC cells to cisplatin by targeting IGF2BP1 and inhibiting AKT signaling pathway [65]. At the same time, NF-κB, a major inducer of stress-response genes, is a ubiquitous transcription factor, and the dysfunction of NF-κB is closely related to different types of cancers. Meanwhile, the increased activation of NF-κB is a predictor of poor disease progression and confers resistance to cell apoptosis [109]. Interestingly, further study reported that miR-708 strongly repressed NF-κB signaling pathway by targeting inhibitor of kappa light polypeptide gene enhancer (kinase-β/IKBKB (IKKβ)) in B cells, which is a key kinase facilitating NF-κB signaling, and contributes to inhibit CLL [76].

Secondly, miRNAs are stronger than single miRNA used alone usually. It was also investigated that CD44 and miR-221 are upregulated in HepG2 and SMMC-7721 cells. The inhibition of miR-221 could indirectly increase the expression of miR-708, finally suppressing the level of CD44 in HCC, then playing a certain anti-cancer role [110]. Chemical drugs have been shown the ability to treat various cancers by regulating the expression of miR-708. For example, Metformin has been used as a first-line antidiabetes drug for decades. Furthermore, Yang et al. identified that metformin promotes increased expression of miR-708-5p, leading to the suppression of endoplasmic reticulum (ER) membrane protein neuronatin (NNAT) expression and subsequently induces apoptosis of PC cells through the ER signaling pathway [111]. Of note, glucocorticoids were displayed a novel activity in the inhibition of OC metastasis. Meanwhile, glucocorticoid treatments induced the expression of miR-708, leading to the suppression of Rap1B, which resulted in the reduction of integrin-mediated focal adhesion formation, inhibition of OC cell migration/invasion and impaired abdominal metastasis in an orthotopic xenograft mouse model [31]. Thus, there are some opportunities for glucocorticoids and their downstream mediators, miR-708 or Rap1B, as therapeutic modalities against metastatic ovarian epithelial cancer. Restoring Rap1B expression reverts glucocorticoid-miR-708 cascade-mediated suppression of OC cell invasion and metastasis [31]. Overall, these findings reveal an opportunity for glucocorticoids and their downstream mediators, miR-708 or Rap1B, as therapeutic modalities against metastatic ovarian epithelial cancer (Fig. 2). Interestingly, in breast cancer, glucocorticoid receptor (GR) agonist activates miR-708 in breast cancerous cells (BCCs) via GRα

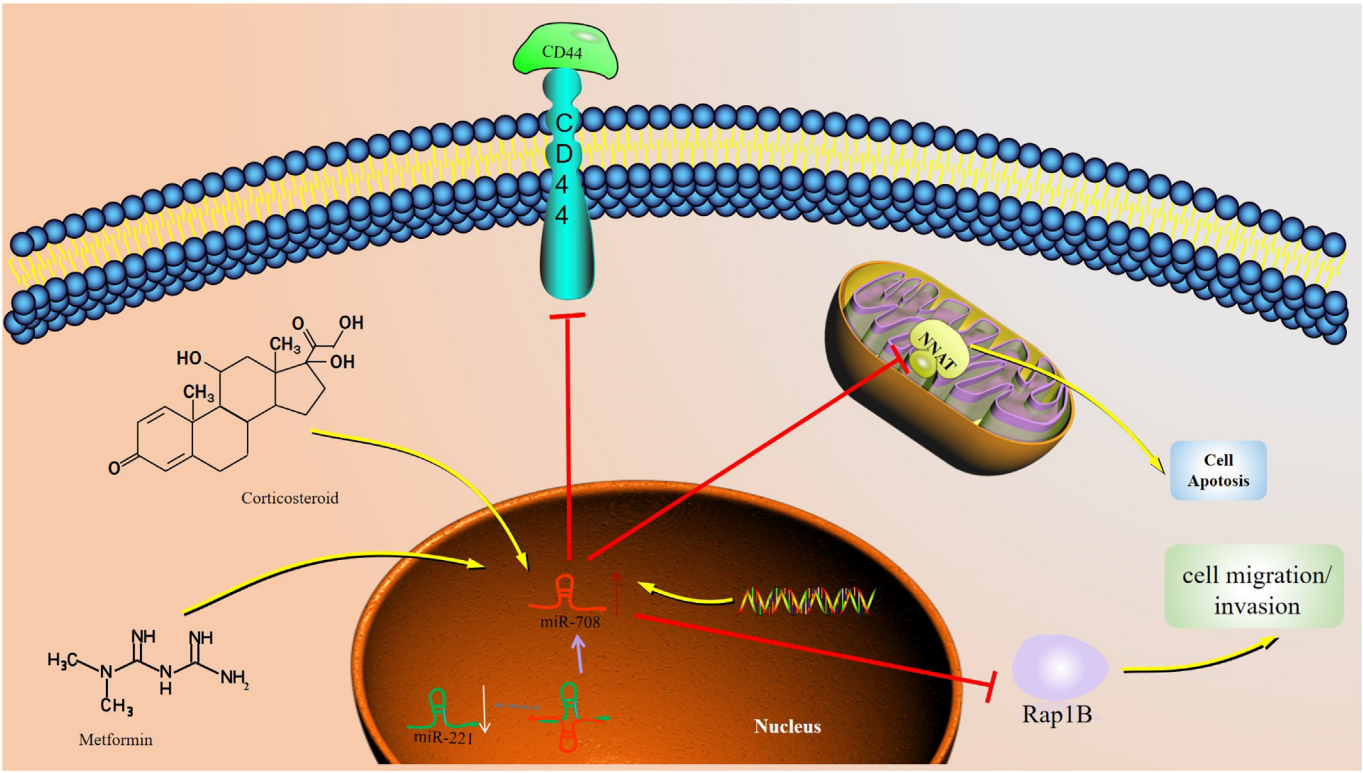

Fig. 2. Other miRNAs and chemical drugs regulated tumorigenesis by mediating the miR-708. Firstly, the inhibition of miR-221 could indirectly increase the expression of miR-708, finally suppressing the level of CD44 in HCC, then playing a certain anti-cancer role. What's more, metformin promotes increased expression of miR-708-5p, leading to the suppression of endoplasmic reticulum (ER) membrane protein neuronatin (NNAT) expression and subsequently induces apoptosis of PC cells through the ER signaling pathway. Finally, glucocorticoids and their downstream mediators, miR-708 or Rap1B, as therapeutic modalities be against metastatic ovarian epithelial cancer.

signaling. Furthermore, it was confirmed that NF-κB activating kinases beta (IKKβ) is a direct target of miR-708, which is activated by GR agonists. GR agonist-mediated activation of miR-708 represses NF-κB downstream target genes. Thus, the migratory and invasive potential of BCCs were inhibited [112].

7. Future expectation

A growing understanding of miR-708 in various cancers open up the possibility of many novel therapeutic strategies. Notably, the expression level of miR-708 was higher in lung cancer, bladder cancer (BC) and colorectal cancer (CRC) cell lines to promote proliferation and promote migration of cancer cells. Additionally, it is well documented that miR-708 could be a tumor suppressor in some cancers. Moreover, accumulating evidence has demonstrated that miR-708 were dysregulated in various cancers and closely related to tumorigenesis, metastasis, and prognosis or diagnosis via some signaling pathway. Of note, it was confirmed that miR-708 acted as a potential new target in cancer treatment and a biomarker for cancer diagnosis. The biological information about miR-708 was far from enough and the therapeutic effect was not very prominent. Thus, additional studies about miR-708 should be done for defining (Fig. 3).

Firstly, some data supported that the combined analyses of the genes outperformed a single one used alone. MiR-708 could be combined with non-coding RNAs (ncRNA) to regulate the progression of various cancers, such as some long non-coding RNAs (lncRNAs) and miRNAs. Of note, ROC analyses were performed that miR-205 and miR-210 combined with miR-708 could provide high diagnostic efficiency for relevant cancer [105]. Thus, other miRNAs also may be a potential gene to treat cancers in combination with miR-708. What's more, lncRNAs were RNA transcripts in eukaryotic cells with > 200 nucleotides in length and without protein-coding capacity. On the other hand, lncRNAs showed the therapeutic effect of cancer by influencing tumor cell proliferation, evading growth suppressors, enabling replicative immortality, enabling replicative immortality, inducing angiogenesis and resisting cell death [113,114]. Luckily, Li et al. confirmed that Long intergenic non-protein-coding RNA 1567 (LINC01567) acts as a "sponge" against microRNA-93 in regulating the proliferation and tumorigenesis of human colon cancer stem cells [115]. Therefore, it offered a possibility that lncRNAs might inhibit the expression of miR-708 to fight the progression of cancers. Of course, it's quite possible that lncRNAs could cooperate with miR-708 to therapy cancer.

Secondly, CRISPR/Cas9 are very robust and straightforward gene editing tools, which has been successfully applied for disruption of protein coding 24 sequences in a variety of organisms [116]. Meanwhile, CRISPR/Cas9 could cause insertion or deletion mutation of target gene. In recent research, CRISPR/Cas9 could be successfully used to target miRNAs and that this system is a valuable alternative to sponge decoy overexpression, negating the requirement for introducing transgenes [117]. What's more, in view of the specificity, efficiency, simplicity and versatility, CRISPR/Cas9 has achieved many successes as a powerful genome engineering tool for the treatment of many diseases [118]. For example, miR-196a is able to restore the aggressive phenotype of annexin A1 knock-out in pancreatic cancer cells by CRISPR/Cas9 genome editing [119]. Therefore, there's a good chance that the technology of CRISPR/Cas9 could be used to treat cancers by editing the expression level of miR-708. Thus, CRISPR/Cas9 might be used to treat cancers by regulating the expression of miR-708 via the relevant molecular mechanism.

Finally, exosomes, a kind of endogenous extracellular vesicle (40–100 nm in diameter), are considered as a new generation of a natural nanoscale delivery system. Exosomes secreted by different types

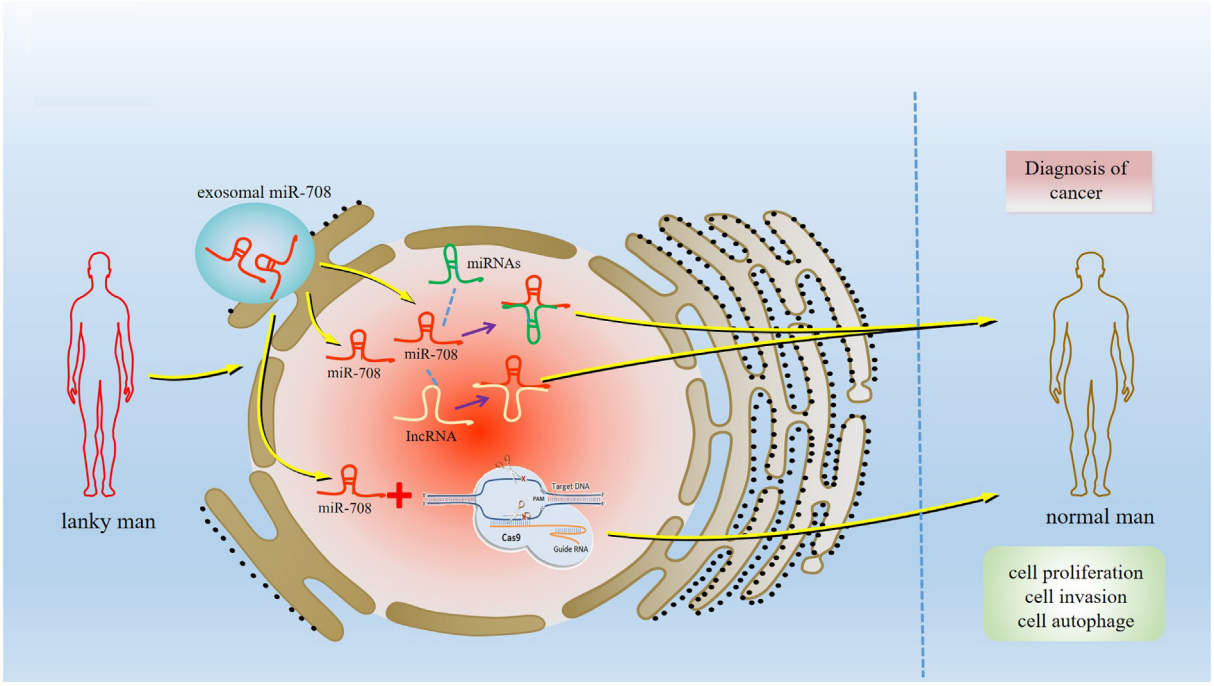

Fig. 3. The future expectation of miR-708 in various cancers.

of cells carry different signaling molecules (such as RNA and protein), so they have great potential for targeting drug delivery and treatment [120,121]. At the same time, exosome-based therapies have emerged over the past decade as an attractive strategy for tissue repair, immune vaccine and against cancer [122]. Of note, exosomal miRNAs have been demonstrated as promising and new biomarkers in cancer screening, diagnosis and prognosis [123]. Furthermore, Zhai et al. developed a BC diagnostic assay using the gold nanoflare probe to detect plasma exosomal miR-1246 level as a biomarker. At the same time, it was confirmed that plasma exosomal miR-1246 is indeed a robust biomarker to differentiate BC patients from normal individuals [124]. Therefore, the expression of miR-708 was increased through exosomal miR-708, thus, which plays an important role in cancer prevention, diagnosis and treatment.

8. Conclusion

Accumulating evidence has demonstrated that miR-708 plays a regulatory role in a variety of cellular processes, physiological responses, and human diseases, particularly cancer [9,124]. Multiple studies implicated important roles of the miR-708 in cancer, including survival, proliferation, growth, migration, invasion, EMT, metastasis, diagnosis and prognosis [10,36,44]. Moreover, miR-708 was involved in the regulation of signaling pathways in cancer cells. In lung cancer, miR-708 modulates cell proliferation by regulating Wnt/β-catenin signaling pathway [94]. In CRC, lung cancer and BC, miR-708 is highly expressed in primary tumors to promote the proliferation of cancer cells, but in PC, HCC, GC and so on, the expression of miR-708 is reduced, which is beneficial to its migration and invasion [36,101]. Taken together, the above studies indicated that miR-708 exerts significant regulatory functions in tumor development. Undoubtedly, larger sample investigations and more precise mechanisms will be the research trend and emphasis in the future. It is hopeful that miR-708 will ultimately achieve clinical application.

Declaration of Competing Interest

None.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (Nos. 81700522, 81602344), Natural Science Foundation of Anhui Province (1808085MH235), Grants for Scientific Research of BSKY (XJ201624), Natural Science Foundation of Colleges and Universities in Anhui Province (KJ2018A0845).

References

[1] S. Noorolyai, A. Mokhtarzadeh, E. Baghbani, M. Asadi, A. Baghbanzadeh Kojabad, M.M. Mogaddam, B. Baradaran, The role of microRNAs involved in PI3-kinase signaling pathway in colorectal cancer, J. Cell. Physiol. 234 (5) (2019) 5664–5673.
[2] S. Kumar, S.K. Sharawat, Epigenetic regulators of programmed death-ligand 1 expression in human cancers, Transl. Res. 202 (2018) 129–145.
[3] A.C. Uscanga-Palomeque, K.M. Calvillo-Rodriguez, L. Gomez-Morales, E. Larde, T. Denefle, D. Caballero-Hernandez, H. Merle-Beral, S.A. Susin, P. Karoyan, A.C. Martinez-Torres, C. Rodriguez-Padilla, CD47 agonist peptide PKHB1 induces immunogenic cell death in T-cell acute lymphoblastic leukemia cells, Cancer Sci. 110 (1) (2019) 256–268.
[4] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[5] L. Yan, F. Xu, C.L. Dai, Relationship between epithelial-to-mesenchymal transition and the inflammatory microenvironment of hepatocellular carcinoma, J. Exp. Clin. Cancer Res. 37 (1) (2018) 203.
[6] N.J. Monteleone, C.S. Lutz, miR-708-5p: a microRNA with emerging roles in cancer, Oncotarget 8 (41) (2017) 71292–71316.
[7] X. Wu, T. Liu, O. Fang, W. Dong, F. Zhang, L. Leach, X. Hu, Z. Luo, MicroRNA-708-5p acts as a therapeutic agent against metastatic lung cancer, Oncotarget 7 (3) (2016) 2417–2432.
[8] D. Liu, B. Wang, Y. Zhu, F. Yan, W. Dong, Carnosic acid regulates cell proliferation and invasion in chronic myeloid leukemia cancer cells via suppressing microRNA-708, J. BUON 23 (3) (2018) 741–746.
[9] X. Li, X. Zhong, X. Pan, Y. Ji, Tumor suppressive microRNA-708 targets Notch1 to suppress cell proliferation and invasion in gastric cancer, Oncol. Res. 26 (2018) 1317–1326.
[10] J.W. Lee, W. Guan, S. Han, D.K. Hong, L.S. Kim, H. Kim, MicroRNA-708-3p mediates metastasis and chemoresistance through inhibition of epithelial-to-mesenchymal transition in breast cancer, Cancer Sci. 109 (5) (2018) 1404–1413.
[11] J. Ferlay, M. Colombet, I. Soerjomataram, C. Mathers, D.M. Parkin, M. Pineros, A. Znaor, F. Bray, Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods, Int. J. Cancer 144 (8) (2019) 1941–1953.
[12] X. Li, Y. Deng, W. Tang, Q. Sun, Y. Chen, C. Yang, B. Yan, Y. Wang, J. Wang, S. Wang, F. Yang, Y. Ding, G. Zhao, G. Cao, Urban-rural disparity in cancer incidence, mortality, and survivals in Shanghai, China, during 2002 and 2015,

Front. Oncol. 8 (2018) 579.
[13] J. Li, L. Shi, H. Liang, G. Ding, L. Xu, Urban-rural disparities in health care utilization among Chinese adults from 1993 to 2011, BMC Health Serv. Res. 18 (1) (2018) 102.
[14] D. Mossmann, S. Park, M.N. Hall, mTOR signalling and cellular metabolism are mutual determinants in cancer, Nat. Rev. Cancer 18 (12) (2018) 744–757.
[15] V.J.N. Bykov, S.E. Eriksson, J. Bianchi, K.G. Wiman, Targeting mutant p53 for efficient cancer therapy, Nat. Rev. Cancer 18 (2) (2018) 89–102.
[16] P.M. Comoglio, L. Trusolino, C. Boccaccio, Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy, Nat. Rev. Cancer 18 (6) (2018) 341–358.
[17] P. Lagergren, A. Schandl, N.K. Aaronson, H.O. Adami, F. de Lorenzo, L. Denis, S. Faithfull, L. Liu, F. Meunier, C. Ulrich, S. European Academy of Cancer, Cancer survivorship: an integral part of Europe's research agenda, Mol. Oncol. 13 (3) (2019) 624–635.
[18] C. White, T. Nimeh, G.S. Gazelle, M.C. Weinstein, K.R. Loughlin, A decision analysis comparing 3 active surveillance protocols for the treatment of patients with low-risk prostate cancer, Cancer 125 (6) (2019) 952–962.
[19] J. Shen, S. Cao, X. Sun, B. Pan, J. Cao, D. Che, S. Jin, Y. Cao, Y. Tian, Y. Yu, Sinoporphyrin sodium-mediated Sonodynamic therapy inhibits RIP3 expression and induces apoptosis in the H446 small cell lung cancer cell line, Cell. Physiol. Biochem. 51 (6) (2018) 2938–2954.
[20] R.F. Schlenk, D. Weber, W. Fiedler, H.R. Salih, G. Wulf, H. Salwender, T. Schroeder, T. Kindler, M. Lubbert, D. Wolf, J. Westermann, D. Kraemer, K.S. Gotze, H.A. Horst, J. Krauter, M. Girschikofsky, M. Ringhoffer, T. Sudhoff, G. Held, H.G. Derigs, R. Schroers, R. Greil, M. Griesshammer, E. Lange, A. Burchardt, U. Martens, B. Hertenstein, L. Marretta, M. Heuser, F. Thol, V.I. Gaidzik, W. Herr, J. Krzykalla, A. Benner, K. Dohner, A. Ganser, P. Paschka, H. Dohner, A.M.L.S.G. German-Austrian, Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD, Blood 133 (8) (2019) 840–851.
[21] C. Vellani, D. D'Ambrosio, L. Licata, I. Vacchieri, A. Bernardo, G. Trifiro, Monitoring response of advanced Merkel cell carcinoma to Avelumab with (18)F-FDG PET/CT, Eur. J. Nucl. Med. Mol. Imaging 46 (5) (2019) 1197–1198.
[22] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeno, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, M. Ozguroglu, P. Investigators, Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (20) (2017) 1919–1929.
[23] J.M.O. Santos, S. Peixoto da Silva, N.R. Costa, R.M. Gil da Costa, R. Medeiros, The role of microRNAs in the metastatic process of high-risk HPV-induced cancers, Cancers 10 (12) (2018).
[24] G. Li, F. Yang, H. Xu, Z. Yue, X. Fang, J. Liu, MicroRNA-708 is downregulated in hepatocellular carcinoma and suppresses tumor invasion and migration, Biomed. Pharmacother. 73 (2015) 154–159.
[25] M.B. Baghdadi, J. Firmino, K. Soni, B. Evano, D. Di Girolamo, P. Mourikis, D. Castel, S. Tajbakhsh, Notch-induced miR-708 antagonizes satellite cell migration and maintains quiescence, Cell Stem Cell 23 (6) (2018) 859-868 e5.
[26] T. Bohn, S. Rapp, N. Luther, M. Klein, T.J. Bruehl, N. Kojima, P. Aranda Lopez, J. Hahlbrock, S. Muth, S. Endo, S. Pektor, A. Brand, K. Renner, V. Popp, K. Gerlach, D. Vogel, C. Lueckel, D. Arnold-Schild, J. Pouyssegur, M. Kreutz, M. Huber, J. Koenig, B. Weigmann, H.C. Probst, E. von Stebut, C. Becker, H. Schild, E. Schmitt, T. Bopp, Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages, Nat. Immunol. 19 (12) (2018) 1319–1329.
[27] Y. Gao, F. Souza-Fonseca-Guimaraes, T. Bald, S.S. Ng, A. Young, S.F. Ngiow, J. Rautela, J. Straube, N. Waddell, S.J. Blake, J. Yan, L. Bartholin, J.S. Lee, E. Vivier, K. Takeda, M. Messaoudene, L. Zitvogel, M.W.L. Teng, G.T. Belz, C.R. Engwerda, N.D. Huntington, K. Nakamura, M. Holzel, M.J. Smyth, Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells, Nat. Immunol. 18 (9) (2017) 1004–1015.
[28] J. Wu, W. Fan, L. Ma, X. Geng, miR-708-5p promotes fibroblast-like synoviocytes' cell apoptosis and ameliorates rheumatoid arthritis by the inhibition of Wnt3a/beta-catenin pathway, Drug Des. Dev. Ther. 12 (2018) 3439–3447.
[29] W. Huang, W.T. Wang, K. Fang, Z.H. Chen, Y.M. Sun, C. Han, L.Y. Sun, X.Q. Luo, Y.Q. Chen, MIR-708 promotes phagocytosis to eradicate T-ALL cells by targeting CD47, Mol. Cancer 17 (1) (2018) 12.
[30] M.A. Cortez, S. Anfossi, R. Ramapriyan, H. Menon, S.C. Atalar, M. Aliru, J. Welsh, G.A. Calin, Role of miRNAs in immune responses and immunotherapy in cancer, Genes Chromosom. Cancer 58 (4) (2019) 244–253.
[31] K.T. Lin, Y.M. Yeh, C.M. Chuang, S.Y. Yang, J.W. Chang, S.P. Sun, Y.S. Wang, K.C. Chao, L.H. Wang, Glucocorticoids mediate induction of microRNA-708 to suppress ovarian cancer metastasis through targeting Rap1B, Nat. Commun. 6 (2015) 5917.
[32] K. Guo, Z. Liang, F. Li, H. Wang, Comparison of miRNA and gene expression profiles between metastatic and primary prostate cancer, Oncol. Lett. 14 (5) (2017) 6085–6090.
[33] P. Leidinger, M. Hart, C. Backes, S. Rheinheimer, B. Keck, B. Wullich, A. Keller, E. Meese, Differential blood-based diagnosis between benign prostatic hyperplasia and prostate cancer: miRNA as source for biomarkers independent of PSA level, Gleason score, or TNM status, Tumour Biol. 37 (8) (2016) 10177–10185.
[34] C.E. Bayne, S.B. Williams, M.R. Cooperberg, M.E. Gleave, M. Graefen, F. Montorsi, G. Novara, M.C. Smaldone, P. Sooriakumaran, P.N. Wiklund, B.F. Chapin, Treatment of the primary tumor in metastatic prostate cancer: current concepts and future perspectives, Eur. Urol. 69 (5) (2016) 775–787.
[35] W. Chen, P. Li, Y. Liu, Y. Yang, X. Ye, F. Zhang, H. Huang, Isoalantolactone induces apoptosis through ROS-mediated ER stress and inhibition of STAT3 in prostate cancer cells, J. Exp. Clin. Cancer Res. 37 (1) (2018) 309.
[36] S. Saini, S. Majid, V. Shahryari, S. Arora, S. Yamamura, I. Chang, M.S. Zaman, G. Deng, Y. Tanaka, R. Dahiya, miRNA-708 control of CD44(+) prostate cancer-initiating cells, Cancer Res. 72 (14) (2012) 3618–3630.
[37] J. Yang, C. Lu, J. Wei, Y. Guo, W. Liu, L. Luo, G. Fisch, X. Li, Inhibition of KPNA4 attenuates prostate cancer metastasis, Oncogene 36 (20) (2017) 2868–2878.
[38] D. Llopiz, M. Ruiz, L. Villanueva, T. Iglesias, L. Silva, J. Egea, J.J. Lasarte, P. Pivette, V. Trochon-Joseph, B. Vasseur, G. Dixon, B. Sangro, P. Sarobe, Enhanced anti-tumor efficacy of checkpoint inhibitors in combination with the histone deacetylase inhibitor Belinostat in a murine hepatocellular carcinoma model, Cancer Immunol. Immunother. 68 (3) (2019) 379–393.
[39] W. Wang, L.J. Zhao, Y.X. Tan, H. Ren, Z.T. Qi, Identification of deregulated miRNAs and their targets in hepatitis B virus-associated hepatocellular carcinoma, World J. Gastroenterol. 18 (38) (2012) 5442–5453.
[40] K.S. Furtado, F. de Oliveira Andrade, A. Campos, M.P. Rosim, E. Vargas-Mendez, A. Henriques, A. De Conti, C. Scolastici, L.F. Barbisan, R.F. Carvalho, F.S. Moreno, beta-ionone modulates the expression of miRNAs and genes involved in the metastatic phenotype of microdissected persistent preneoplastic lesions in rats submitted to hepatocarcinogenesis, Mol. Carcinog. 56 (1) (2017) 184–196.
[41] Y. Liu, H. Zhu, Z. Zhang, C. Tu, D. Yao, B. Wen, R. Jiang, X. Li, P. Yi, J. Zhan, J. Hu, J. Ding, L. Jiang, F. Zhang, Effects of a single transient transfection of Ten-eleven translocation 1 catalytic domain on hepatocellular carcinoma, PLoS One 13 (12) (2018) e0207139.
[42] C. Wu, W. Chen, M. Fang, A. Boye, X. Tao, Y. Xu, S. Hou, Y. Yang, Compound Astragalus and Salvia miltiorrhiza extract inhibits hepatocellular carcinoma progression via miR-145/miR-21 mediated Smad3 phosphorylation, J. Ethnopharmacol. 231 (2019) 98–112.
[43] Q. Li, S. Li, Y. Wu, F. Gao, miRNA-708 functions as a tumour suppressor in hepatocellular carcinoma by targeting SMAD3, Oncol. Lett. 14 (2) (2017) 2552–2558.
[44] W. Yan, S. Wang, Z. Sun, Y. Lin, S. Sun, J. Chen, W. Chen, Identification of microRNAs as potential biomarker for gastric cancer by system biological analysis, Biomed. Res. Int. 2014 (2014) 901428.
[45] C. Ju, Y. Wen, L. Zhang, Q. Wang, L. Xue, J. Shen, C. Zhang, Neoadjuvant chemotherapy based on abraxane/human neutrophils cytopharmaceuticals with radiotherapy for gastric cancer, Small 15 (5) (2019) e1804191.
[46] T.K. Furuya, C.E. Jacob, M.T.P. Tomitao, L.C.C. Camacho, M. Ramos, J. Eluf-Neto, V.A.F. Alves, B. Zilberstein, I. Cecconello, U. Ribeiro Jr., R. Chammas, Association between polymorphisms in inflammatory response-related genes and the susceptibility, progression and prognosis of the diffuse histological subtype of gastric cancer, Genes 9 (12) (2018).
[47] C.E. DeSantis, J. Ma, A. Goding Sauer, L.A. Newman, A. Jemal, Breast cancer statistics, 2017, racial disparity in mortality by state, CA Cancer J. Clin. 67 (6) (2017) 439–448.
[48] M.K. Nygren, C. Tekle, V.A. Ingebrigtsen, R. Makela, M. Krohn, M.R. Aure, C.E. Nunes-Xavier, M. Perala, T. Tramm, J. Alsner, J. Overgaard, J.M. Nesland, E. Borgen, A.L. Borresen-Dale, O. Fodstad, K.K. Sahlberg, S.K. Leivonen, Identifying microRNAs regulating B7-H3 in breast cancer: the clinical impact of microRNA-29c, Br. J. Cancer 110 (8) (2014) 2072–2080.
[49] L. Ma, S. Ma, G. Zhao, L. Yang, P. Zhang, Q. Yi, S. Cheng, miR-708/LSD1 axis regulates the proliferation and invasion of breast cancer cells, Cancer Med. 5 (4) (2016) 684–692.
[50] S. Hayami, J.D. Kelly, H.S. Cho, M. Yoshimatsu, M. Unoki, T. Tsunoda, H.I. Field, D.E. Neal, H. Yamaue, B.A. Ponder, Y. Nakamura, R. Hamamoto, Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers, Int. J. Cancer 128 (3) (2011) 574–586.
[51] I.M. Bennani-Baiti, Integration of ERalpha-PELP1-HER2 signaling by LSD1 (KDM1A/AOF2) offers combinatorial therapeutic opportunities to circumventing hormone resistance in breast cancer, Breast Cancer Res. 14 (5) (2012) 112.
[52] P. Gener, D. Rafael, J. Seras-Franzoso, A. Perez, L.A. Pindado, G. Casas, D. Arango, Y. Fernandez, Z.V. Diaz-Riascos, I. Abasolo, S. Schwartz Jr., Pivotal role of AKT2 during dynamic phenotypic change of breast cancer stem cells, Cancers 11 (8) (2019).
[53] Y. Su, J. Lu, X. Chen, C. Liang, P. Luo, C. Qin, J. Zhang, Long non-coding RNA HOTTIP affects renal cell carcinoma progression by regulating autophagy via the PI3K/Akt/Atg13 signaling pathway, J. Cancer Res. Clin. Oncol. 145 (3) (2019) 573–588.
[54] A.S. M., C.R. Delma, K. Manickam, S. Mohan, S.L. Habib, M. Natarajan, Heterozygous Tsc2 (Tsc2+/−) mouse model to study induced renal cancer in response to ionizing radiation at low doses, Carcinogenesis 40 (6) (2019) 782–790.
[55] Y. He, J. Liu, Y. Wang, X. Zhu, Z. Fan, C. Li, H. Yin, Y. Liu, Role of miR-486-5p in regulating renal cell carcinoma cell proliferation and apoptosis via TGF-beta-activated kinase 1, J. Cell. Biochem. 120 (3) (2019) 2954–2963.
[56] P. Cao, L. Zhou, J. Zhang, F. Zheng, H. Wang, D. Ma, J. Tian, Comprehensive expression profiling of microRNAs in laryngeal squamous cell carcinoma, Head Neck 35 (5) (2013) 720–728.
[57] G. Pentheroudakis, Y. Spector, D. Krikelis, V. Kotoula, E. Meiri, V. Malamou-Mitsi, G. Fountzilas, M. Sanden, N. Pavlidis, H. Benjamin, R. Aharonov, Global microRNA profiling in favorable prognosis subgroups of cancer of unknown primary (CUP) demonstrates no significant expression differences with metastases of matched known primary tumors, Clin. Exp. Metastasis 30 (4) (2013) 431–439.
[58] S. Saini, S. Yamamura, S. Majid, V. Shahryari, H. Hirata, Y. Tanaka, R. Dahiya,

MicroRNA-708 induces apoptosis and suppresses tumorigenicity in renal cancer cells, Cancer Res. 71 (19) (2011) 6208–6219.
[59] M.Y. Jeon, K.J. Min, S.M. Woo, S.U. Seo, Y.H. Choi, S.H. Kim, D.E. Kim, T.J. Lee, S. Kim, J.W. Park, T.K. Kwon, Maritoclax enhances TRAIL-induced apoptosis via CHOP-mediated upregulation of DR5 and miR-708-mediated downregulation of cFLIP, Molecules 23 (11) (2018).
[60] E.A. Kim, S.W. Kim, J. Nam, E.G. Sung, I.H. Song, J.Y. Kim, T.K. Kwon, T.J. Lee, Inhibition of c-FLIPL expression by miRNA-708 increases the sensitivity of renal cancer cells to anti-cancer drugs, Oncotarget 7 (22) (2016) 31832–31846.
[61] B. Zheng, H. Shen, H. Han, T. Han, Y. Qin, Dietary fiber intake and reduced risk of ovarian cancer: a meta-analysis, Nutr. J. 17 (1) (2018) 99.
[62] K. Lindemann, P.J. Beale, E. Rossi, J.C. Goh, M.M. Vaughan, M.E. Tenney, J.K. Martyn, D. Sommeijer, J.L. Iglesias, G. Kremmidiotis, J. Simpson, E. Doolin, T.C. Lavranos, A. Leske, A.S. Veillard, D. Espinoza, M.R. Stockler, D. Rischin, A. For, H.C. Groups, Phase I study of BNC105P, carboplatin and gemcitabine in partially platinum-sensitive ovarian cancer patients in first or second relapse (ANZGOG-1103), Cancer Chemother. Pharmacol. 83 (1) (2019) 97–105.
[63] S. Dasari, Y. Fang, A.K. Mitra, Cancer associated fibroblasts: naughty neighbors that drive ovarian cancer progression, Cancers 10 (11) (2018).
[64] T.Z. Tan, V. Heong, J. Ye, D. Lim, J. Low, M. Choolani, C. Scott, D.S.P. Tan, R.Y. Huang, Decoding transcriptomic intra-tumour heterogeneity to guide personalised medicine in ovarian cancer, J. Pathol. 247 (3) (2019) 305–319.
[65] X. Qin, L. Sun, J. Wang, Restoration of microRNA-708 sensitizes ovarian cancer cells to cisplatin via IGF2BP1/Akt pathway, Cell Biol. Int. 41 (10) (2017) 1110–1118.
[66] E. Asselin, G.B. Mills, B.K. Tsang, XIAP regulates Akt activity and caspase-3-dependent cleavage during cisplatin-induced apoptosis in human ovarian epithelial cancer cells, Cancer Res. 61 (5) (2001) 1862–1868.
[67] L. Carminati, D. Pinessi, P. Borsotti, L. Minoli, R. Giavazzi, M. D'Incalci, D. Belotti, G. Taraboletti, Antimetastatic and antiangiogenic activity of trabectedin in cutaneous melanoma, Carcinogenesis 40 (2) (2019) 303–312.
[68] C. Rinner, E. Helm, R. Dunkl, H. Kittler, S. Rinderle-Ma, Process mining and conformance checking of long running processes in the context of melanoma surveillance, Int. J. Environ. Res. Public Health 15 (12) (2018).
[69] L.W. Pfannenstiel, C. McNeilly, C. Xiang, K. Kang, C.M. Diaz-Montero, J.S. Yu, B.R. Gastman, Combination PD-1 blockade and irradiation of brain metastasis induces an effective abscopal effect in melanoma, Oncoimmunology 8 (1) (2019) e1507669.
[70] T. Murakami, I. Saitoh, M. Sato, E. Inada, M. Soda, M. Oda, H. Domon, Y. Iwase, T. Sawami, K. Matsueda, Y. Terao, H. Ohshima, H. Noguchi, H. Hayasaki, Isolation and characterization of lymphoid enhancer factor-1-positive deciduous dental pulp stem-like cells after transfection with a piggyBac vector containing LEF1 promoter-driven selection markers, Arch. Oral Biol. 81 (2017) 110–120.
[71] X.F. Song, Q.H. Wang, R. Huo, Effects of microRNA-708 on epithelial-mesenchymal transition, cell proliferation and apoptosis in melanoma cells by targeting LEF1 through the Wnt signaling pathway, Pathol. Oncol. Res. 25 (1) (2019) 377–389.
[72] H.J. Lu, J. Yan, P.Y. Jin, G.H. Zheng, H.L. Zhang, M. Bai, D.M. Wu, J. Lu, Y.L. Zheng, Mechanism of microRNA-708 targeting BAMBI in cell proliferation, migration, and apoptosis in mice with melanoma via the Wnt and TGF-beta signaling pathways, Technol. Cancer Res. Treat. 17 (2018) 1533034618756784.
[73] Y. Zou, W. Xu, J. Li, Chimeric antigen receptor-modified T cell therapy in chronic lymphocytic leukemia, J. Hematol. Oncol. 11 (1) (2018) 130.
[74] S. Dong, B.K. Harrington, E.Y. Hu, J.T. Greene, A.M. Lehman, M. Tran, R.L. Wasmuth, M. Long, N. Muthusamy, J.R. Brown, A.J. Johnson, J.C. Byrd, PI3K p110delta inactivation antagonizes chronic lymphocytic leukemia and reverses T cell immune suppression, J. Clin. Invest. 129 (1) (2019) 122–136.
[75] L. Mansouri, N. Papakonstantinou, S. Ntoufa, K. Stamatopoulos, R. Rosenquist, NF-kappaB activation in chronic lymphocytic leukemia: a point of convergence of external triggers and intrinsic lesions, Semin. Cancer Biol. 39 (2016) 40–48.
[76] C. Baer, C.C. Oakes, A.S. Ruppert, R. Claus, S.Z. Kim-Wanner, D. Mertens, T. Zenz, S. Stilgenbauer, J.C. Byrd, C. Plass, Epigenetic silencing of miR-708 enhances NF-kappaB signaling in chronic lymphocytic leukemia, Int. J. Cancer 137 (6) (2015) 1352–1361.
[77] F. Duffaud, O. Mir, P. Boudou-Rouquette, S. Piperno-Neumann, N. Penel, E. Bompas, C. Delcambre, E. Kalbacher, A. Italiano, O. Collard, C. Chevreau, E. Saada, N. Isambert, J. Delaye, C. Schiffler, C. Bouvier, V. Vidal, S. Chabaud, J.Y. Blay, G. French Sarcoma, Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study, Lancet Oncol. 20 (1) (2019) 120–133.
[78] L. Lin, M. Huang, X. Shi, A. Mayakonda, K. Hu, Y.Y. Jiang, X. Guo, L. Chen, B. Pang, N. Doan, J.W. Said, J. Xie, S. Gery, X. Cheng, Z. Lin, J. Li, B.P. Berman, D. Yin, D.C. Lin, H.P. Koeffler, Super-enhancer-associated MEIS1 promotes transcriptional dysregulation in Ewing sarcoma in co-operation with EWS-FLI1, Nucleic Acids Res. 47 (3) (2019) 1255–1267.
[79] P. Puerto-Camacho, A.T. Amaral, S.E. Lamhamedi-Cherradi, B.A. Menegaz, H. Castillo-Ecija, J.L. Ordonez, S. Dominguez, C. Jordan-Perez, J. Diaz-Martin, L. Romero-Perez, M. Lopez-Alvarez, G. Civantos-Jubera, M.J. Robles-Frias, M. Biscuola, C. Ferrer, J. Mora, B. Cuglievan, K. Schadler, O. Seifert, R. Kontermann, K. Pfizenmaier, L. Simon, M. Fabre, A.M. Carcaboso, J.A. Ludwig, E. de Alava, Preclinical Efficacy of Endoglin-Targeting Antibody-Drug Conjugates for the Treatment of Ewing Sarcoma, Clin. Cancer Res. 25 (7) (2019) 2228–2240.
[80] O. Delattre, J. Zucman, T. Melot, X.S. Garau, J.M. Zucker, G.M. Lenoir, P.F. Ambros, D. Sheer, C. Turc-Carel, T.J. Triche, et al., The Ewing family of tumors–a subgroup of small-round-cell tumors defined by specific chimeric transcripts, N. Engl. J. Med. 331 (5) (1994) 294–299.
[81] T.P. Robin, A. Smith, E. McKinsey, L. Reaves, P. Jedlicka, H.L. Ford, EWS/FLI1 regulates EYA3 in Ewing sarcoma via modulation of miRNA-708, resulting in increased cell survival and chemoresistance, Mol. Cancer Res. 10 (8) (2012) 1098–1108.
[82] G.M. Roberto, G.M. Vieira, L.E.A. Delsin, M.O. Silva, R.G. Hakime, E.E. Engel, C.A. Scrideli, L.G. Tone, M.S. Brassesco, MiR-708-5p is inversely associated with EWS/FLI1 Ewing sarcoma but does not represent a prognostic predictor, Cancer Gene Ther. 230 (2019) 21–27.
[83] X. Shi, M. Fan, Tip60-dependent acetylation of KDM2B promotes osteosarcoma carcinogenesis, J. Cell. Mol. Med. (2019), https://doi.org/10.1111/jcmm.14497 [Epub ahead of print].
[84] J. Wang, C. Hu, J. Wang, Y. Shen, Q. Bao, F. He, H. Wang, L. Gong, Z. Liu, F. Hu, J. Liang, Q. Zhou, L. Wei, J. Wen, W. Zhang, Checkpoint blockade in combination with doxorubicin augments tumor cell apoptosis in osteosarcoma, J. Immunother. (2019), https://doi.org/10.1097/CJI.0000000000000281 [Epub ahead of print].
[85] S. Wu, Z. Gu, Y. Wu, W. Wu, B. Mao, S. Zhao, LINC00324 accelerates the proliferation and migration of osteosarcoma through regulating WDR66, J. Cell. Physiol. (2019), https://doi.org/10.1002/jcp.28973 [Epub ahead of print].
[86] C. Sui, D. Liu, Y. Hu, L. Zhang, MicroRNA-708-5p affects proliferation and invasion of osteosarcoma cells by targeting URGCP, Exp. Ther. Med. 17 (3) (2019) 2235–2241.
[87] J.Y. Fu, Y.L. Wan, T.Y. Huang, C.F. Wu, Y.H. Liu, M.J. Hsieh, Y.C. Wu, C.Y. Wu, Correlation between image characteristics and pathologic findings in non small cell lung cancer patients after anatomic resection, PLoS One 13 (10) (2018) e0206386.
[88] H.C. Stamatakis, R. Steegman, J. Dusseldorp, Y. Ren, Head positioning in a cone beam computed tomography unit and the effect on accuracy of the three-dimensional surface mode, Eur. J. Oral Sci. 127 (1) (2019) 72–80.
[89] Y. Niu, M. Su, Y. Wu, L. Fu, K. Kang, Q. Li, L. Li, G. Hui, F. Li, D. Gou, Circulating plasma miRNAs as potential biomarkers of non-small cell lung cancer obtained by high-throughput real-time PCR profiling, Cancer Epidemiol. Biomark. Prev. 28 (2) (2019) 327–336.
[90] Y. Wang, J. Wang, J. Meng, G. Ding, Z. Shi, R. Wang, X. Zhang, Detection of non-small cell lung cancer cells based on microfluidic polarization microscopic image analysis, Electrophoresis (2018), https://doi.org/10.1002/elps.201800284 [Epub ahead of print].
[91] D. Cao, H. Xu, X. Xu, T. Guo, W. Ge, A reliable and feasible way to predict the benefits of Nivolumab in patients with non-small cell lung cancer: a pooled analysis of 14 retrospective studies, Oncoimmunology 7 (11) (2018) e1507262.
[92] W. Jing, N. Song, Y.P. Liu, X.J. Qu, Y.F. Qi, C. Li, K.Z. Hou, X.F. Che, X.H. Yang, DNMT3a promotes proliferation by activating the STAT3 signaling pathway and depressing apoptosis in pancreatic cancer, Cancer Manag. Res. 11 (2019) 6379–6396.
[93] A.K. Siraj, P. Pratheeshkumar, S.K. Parvathareddy, R. Bu, T. Masoodi, K. Iqbal, M. Al-Rasheed, F. Al-Dayel, S.S. Al-Sobhi, A.S. Alzahrani, M. Al-Dawish, K.S. Al-Kuraya, Prognostic significance of DNMT3A alterations in Middle Eastern papillary thyroid carcinoma, Eur. J. Cancer 117 (2019) 133–144.
[94] T. Liu, X. Wu, T. Chen, Z. Luo, X. Hu, Downregulation of DNMT3A by miR-708-5p inhibits lung cancer stem cell-like phenotypes through repressing Wnt/beta-catenin signaling, Clin. Cancer Res. 24 (7) (2018) 1748–1760.
[95] J.C. Oliveira, M.S. Brassesco, A.G. Morales, J.A. Pezuk, P.F. Fedatto, G.N. da Silva, C.A. Scrideli, L.G. Tone, MicroRNA-100 acts as a tumor suppressor in human bladder carcinoma 5637 cells, Asian Pacific J. Cancer Prev. 12 (11) (2011) 3001–3004.
[96] S. Zhen, J. Lu, W. Chen, L. Zhao, X. Li, Synergistic antitumor effect on bladder cancer by rational combination of programmed cell death 1 blockade and CRISPR-Cas9-mediated long non-coding RNA urothelial carcinoma associated 1 knockout, Hum. Gene Ther. 29 (12) (2018) 1352–1363.
[97] N. Aghaalikhani, N. Rashtchizadeh, P. Shadpour, A. Allameh, M. Mahmoodi, Cancer stem cells as a therapeutic target in bladder cancer, J. Cell. Physiol. 234 (4) (2019) 3197–3206.
[98] T. Song, X. Zhang, L. Zhang, J. Dong, W. Cai, J. Gao, B. Hong, miR-708 promotes the development of bladder carcinoma via direct repression of Caspase-2, J. Cancer Res. Clin. Oncol. 139 (7) (2013) 1189–1198.
[99] Y. Cha, S.Y. Kim, H.Y. Yeo, J.Y. Baek, M.K. Choi, K.H. Jung, S.M. Dong, H.J. Chang, Association of CHFR promoter methylation with treatment outcomes of irinotecan-based chemotherapy in metastatic colorectal cancer, Neoplasia 21 (1) (2019) 146–155.
[100] C. Li, J. Bu, Y. Liao, J. Zhang, J. Han, H. Zhang, H. Xing, Z. Li, H. Wu, L. Liang, M. Wang, W. Qin, T. Yang, High expressions of CUL4A and TP53 in colorectal cancer predict poor survival, Cell. Physiol. Biochem. 51 (6) (2018) 2829–2842.
[101] S.L. Lei, H. Zhao, H.L. Yao, Y. Chen, Z.D. Lei, K.J. Liu, Q. Yang, Regulatory roles of microRNA-708 and microRNA-31 in proliferation, apoptosis and invasion of colorectal cancer cells, Oncol. Lett. 8 (4) (2014) 1768–1774.
[102] E.A. Hungate, S.R. Vora, E.R. Gamazon, T. Moriyama, T. Best, I. Hulur, Y. Lee, T.J. Evans, E. Ellinghaus, M. Stanulla, J. Rudant, L. Orsi, J. Clavel, E. Milne, R.J. Scott, C.H. Pui, N.J. Cox, M.L. Loh, J.J. Yang, A.D. Skol, K. Onel, A variant at 9p21.3 functionally implicates CDKN2B in paediatric B-cell precursor acute lymphoblastic leukaemia aetiology, Nat. Commun. 7 (2016) 10635.
[103] Correction: miRNA-708 control of CD44(+) prostate cancer-initiating cells, Cancer Res. 78 (12) (2018) 3404.
[104] S. Molina-Pinelo, G. Gutierrez, M.D. Pastor, M. Hergueta, G. Moreno-Bueno, R. Garcia-Carbonero, A. Nogal, R. Suarez, A. Salinas, F. Pozo-Rodriguez, F. Lopez-Rios, M.T. Agullo-Ortuno, I. Ferrer, A. Perpina, J. Palacios, A. Carnero, L. Paz-Ares, MicroRNA-dependent regulation of transcription in non-small cell lung cancer, PLoS One 9 (3) (2014) e90524.

[105] L. Xing, N.W. Todd, L. Yu, H. Fang, F. Jiang, Early detection of squamous cell lung cancer in sputum by a panel of microRNA markers, Mod. Pathol. 23 (8) (2010) 1157–1164.
[106] L. Yu, N.W. Todd, L. Xing, Y. Xie, H. Zhang, Z. Liu, H. Fang, J. Zhang, R.L. Katz, F. Jiang, Early detection of lung adenocarcinoma in sputum by a panel of microRNA markers, Int. J. Cancer 127 (12) (2010) 2870–2878.
[107] X.Y. Hu, P.F. Hou, T.T. Li, H.Y. Quan, M.L. Li, T. Lin, J.J. Liu, J. Bai, J.N. Zheng, The roles of Wnt/beta-catenin signaling pathway related lncRNAs in cancer, Int. J. Biol. Sci. 14 (14) (2018) 2003–2011.
[108] Z. Wang, Y. Wang, S. Zhu, Y. Liu, X. Peng, S. Zhang, Z. Zhang, Y. Qiu, M. Jin, R. Wang, Y. Zhong, D. Kong, DT-13 inhibits proliferation and metastasis of human prostate cancer cells through blocking PI3K/Akt pathway, Front. Pharmacol. 9 (2018) 1450.
[109] Q. Liu, W. Tan, J. Che, D. Yuan, L. Zhang, Y. Sun, X. Yue, L. Xiao, Y. Jin, 12-HETE facilitates cell survival by activating the integrin-linked kinase/NF-kappaB pathway in ovarian cancer, Cancer Manag. Res. 10 (2018) 5825–5838.
[110] J. Kim, J. Jiang, M. Badawi, T.D. Schmittgen, miR-221 regulates CD44 in hepatocellular carcinoma through the PI3K-AKT-mTOR pathway, Biochem. Biophys. Res. Commun. 487 (3) (2017) 709–715.
[111] J. Yang, J. Wei, Y. Wu, Z. Wang, Y. Guo, P. Lee, X. Li, Metformin induces ER stress-dependent apoptosis through miR-708-5p/NNAT pathway in prostate cancer, Oncogenesis 4 (2015) e158.
[112] K.J. Senthil Kumar, M. Gokila Vani, H.W. Hsieh, C.C. Lin, J.W. Liao, P.J. Chueh, S.Y. Wang, MicroRNA-708 activation by glucocorticoid receptor agonists regulate breast cancer tumorigenesis and metastasis via downregulation of NF-kappaB signaling, Carcinogenesis 40 (2) (2019) 335–348.
[113] H. Feng, B. Wei, Y. Zhang, Long non-coding RNA HULC promotes proliferation, migration and invasion of pancreatic cancer cells by down-regulating microRNA-15a, Int. J. Biol. Macromol. 126 (2019) 891–898.
[114] Y. Lou, Y. Yu, X. Xu, S. Zhou, H. Shen, T. Fan, D. Wu, J. Yin, G. Li, Long non-coding RNA LUCAT1 promotes tumourigenesis by inhibiting ANXA2 phosphorylation in hepatocellular carcinoma, J. Cell. Mol. Med. 23 (3) (2019) 1873–1884.
[115] X. Yu, L. Mi, J. Dong, J. Zou, Long intergenic non-protein-coding RNA 1567 (LINC01567) acts as a "sponge" against microRNA-93 in regulating the proliferation and tumorigenesis of human colon cancer stem cells, BMC Cancer 17 (1) (2017) 716.
[116] M. Li, X. Liu, S. Dai, H. Xiao, D. Wang, High efficiency targeting of non-coding sequences using CRISPR/Cas9 system in tilapia, G3 9 (1) (2019) 287–295.
[117] K. Kellner, A. Solanki, T. Amann, N. Lao, N. Barron, Targeting miRNAs with CRISPR/Cas9 to improve recombinant protein production of CHO cells, Methods Mol. Biol. 1850 (2018) 221–235.
[118] R. Belvedere, P. Saggese, E. Pessolano, D. Memoli, V. Bizzarro, F. Rizzo, L. Parente, A. Weisz, A. Petrella, miR-196a is able to restore the aggressive phenotype of annexin A1 Knock-out in pancreatic cancer cells by CRISPR/Cas9 genome editing, Int. J. Mol. Sci. 19 (7) (2018).
[119] S. Zhen, L. Hua, Y.H. Liu, X.M. Sun, M.M. Jiang, W. Chen, L. Zhao, X. Li, Inhibition of long non-coding RNA UCA1 by CRISPR/Cas9 attenuated malignant phenotypes of bladder cancer, Oncotarget 8 (6) (2017) 9634–9646.
[120] W. Liao, Y. Du, C. Zhang, F. Pan, Y. Yao, T. Zhang, Q. Peng, Exosomes: the next generation of endogenous nanomaterials for advanced drug delivery and therapy, Acta Biomater. 86 (2019) 1–14.
[121] M. Mathieu, L. Martin-Jaular, G. Lavieu, C. Thery, Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication, Nat. Cell Biol. 21 (1) (2019) 9–17.
[122] A. Gougelet, Exosomal microRNAs as a potential therapeutic strategy in hepatocellular carcinoma, World J. Hepatol. 10 (11) (2018) 785–789.
[123] Y. Yang, E. Kannisto, G. Yu, M.E. Reid, S.K. Patnaik, Y. Wu, An Immuno-biochip selectively captures tumor-derived exosomes and detects exosomal RNAs for cancer diagnosis, ACS Appl. Mater. Interfaces 10 (50) (2018) 43375–43386.
[124] L.Y. Zhai, M.X. Li, W.L. Pan, Y. Chen, M.M. Li, J.X. Pang, L. Zheng, J.X. Chen, W.J. Duan, In situ detection of plasma exosomal microRNA-1246 for breast cancer diagnostics by a Au nanoflare probe, ACS Appl. Mater. Interfaces 10 (46) (2018) 39478–39486.