Pharmacological Research 190 (2023) 106732

Contents lists available at ScienceDirect

Pharmacological Research

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

HMGA2 regulation by miRNAs in cancer: Affecting cancer hallmarks and therapy response

Mehrdad Hashemi [a,b], Mohsen Rashidi [c,d], Kiavash Hushmandi [e], Timo L.M. ten Hagen [f], Shokooh Salimimoghadam [g,*], Afshin Taheriazam [a,h,**], Maliheh Entezari [a,b,**], Mojtaba Falahati [f,*]

[a] Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[b] Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[c] Department Pharmacology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari 4815733971, Iran
[d] The Health of Plant and Livestock Products Research Center, Mazandaran University of Medical Sciences, Sari 4815733971, Iran
[e] Department of Food Hygiene and Quality Control, Division of Epidemiology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
[f] Precision Medicine in Oncology (PrMiO), Department of Pathology, Erasmus MC Cancer Institute, Erasmus MC, Rotterdam, the Netherlands
[g] Department of Biochemistry and Molecular Biology, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
[h] Department of Orthopedics, Faculty of medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

Abbreviations: AP1, activator protein 1; APC, adenomatous polyposis coli; ALDH1, aldehyde dehydrogenase 1; AI, artificial intelligence; ATR, ataxia telangiectasia and Rad3-related protein; ABCB1, ATP-binding cassette sub-family B member 1; ATG5, Autophagy Related 5; BZW1, Basic leucine zipper and W2 domain-containing protein 1; Bcl-2, B-cell lymphoma 2; BCLAF1, Bcl-2-associated transcription factor1; BRCA1, Breast cancer gene 1; CPT1A, Carnitine palmitoyltransferase 1 A; Chk1, Checkpoint kinase 1; CircRNA, Circular RNA; ceRNA, Competing endogenous RNA; CBP, Cyclic adenosine monophosphate Response Element Binding protein Binding Protein; DCTD, Deoxycytidine monophosphate deaminase; DNMT3B, DNA methyltransferases 3 B; E2F1, E2F Transcription Factor 1; EGF-L7, Epidermal growth factor-like protein 7; ESCC, Esophageal squamous cell carcinoma; ER-α36, Estrogen receptor alpha-36; EIF4A2, Eukaryotic initiation factor 4A-II; eIF5A2, Eukaryotic translation initiation factor 5A-2; ERK, Extracellular signal-regulated kinases; FEN1, Flap endonuclease 1; FAK, Focal adhesion kinase; Foxi1, Forkhead box I1; FOXL2, Forkhead box protein L2; GBM, Glioblastoma multiforme; GSK-3β, Glycogen synthase kinase-3β; HNSCC, Head and neck squamous cell carcinoma; HN1, Hematological and neurological expressed 1; HBXIP, Hepatitis B virus X-interacting protein; HCC, Hepatocellular carcinoma; HNF4G, Hepatocyte nuclear factor 4-gamma; HNRNPK, Heterogeneous nuclear ribonucleoprotein K; HOXA9, Homeobox A9; HIF1A, Hypoxia-inducible factor 1-alpha; IKKε, Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Epsilon; KLHL21, Kelch-like protein 21; KRT17, Keratin 17; LAMC2, Laminin subunit gamma-2; LATS1, Large tumor suppressor kinase 1; LSCC, Laryngeal squamous cell carcinoma; LTBP-1, Latent Transforming Growth Factor Beta Binding Protein 1; LncRNA, Long non-coding RNA; mTOR, Mammalian target of rapamycin; MMP2, Matrix metallopeptidase 2; MITF, Melanocyte Inducing Transcription Factor; MET, Mesenchymal-epithelial transition factor; MTA1, Metastasis-associated protein 1; MiRNA, MicroRNA; MAPK, Mitogen-activated protein kinases; SMAD2, Mothers against decapentaplegic homolog 2; MDR-1, Multidrug resistance gene 1; MDM2, Murine double minute 2; NF1, Neurofibromatosis type 1; NETO2, Neuropilin and tolloid-like protein 2; NcRNA, Non-coding RNA; NF-κB1, Nuclear factor kappa-light-chain-enhancer of activated B cells 1; NR3C1, Nuclear receptor subfamily 3, group C, member 1; OSCC, Oral squamous cell carcinoma; OLR1, Oxidized Low Density Lipoprotein Receptor 1; P-gp, P-glycoprotein; PTC, Papillary thyroid carcinoma; PDAC, Pancreatic ductal adenocarcinoma; POSTN, Periostin; PTEN, Phosphatase and Tensin Homolog deleted on Chromosome 10; PI3K, Phosphoinositide 3-kinase; PAICS, Phosphoribosylaminoimidazole carboxylase/phosphoribosylaminoimidazole succinocarboxamide synthetase; PDGFRA, Platelet Derived Growth Factor Receptor Alpha; PCL, Poly (ε-caprolactone); PEG, Polyethylene glycol; PEI, Polyethyleneimine; PLGA, Poly(lactic-co-glycolic acid); PD-L1, Programmed death-ligand 1; PP4R1, Protein phosphatase 4 regulatory subunit 1; RBP1, Retinol-binding protein 1; RKIP, Raf kinase inhibitory protein; ROCK1, Rho-associated protein kinase; SERPINE1, Serpin Family E Member 1; STAT3, Signal transducer and activator of transcription 3; SP1, Specificity protein 1; SOX2, SRY-box 2; SOX4, SRY-related HMG box transcription factor 4; TET1, Ten-eleven translocation methylcytosine dioxygenase 1; TXNIP, Thioredoxin interacting protein; THBS2, Thrombospondin-2; TCF3, Transcription factor 3; TGF-βR1, Transforming growth factor beta receptor I; Tgfbr3, Transforming growth factor beta receptor type 3; TAM, Tumor associated macrophage; TME, Tumor micro-environment; TP53INP1, Tumor protein p53-inducible nuclear protein 1; U2AF2, U2 auxiliary factor 2; VEGFR2, Vascular endothelial growth factor receptor 2; YAP, Yes-associated protein 1; ZEB, Zinc finger E-box-binding homeobox; Snail, Zinc finger protein SNAI1.

* Corresponding authors.
** Corresponding authors at: Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

E-mail addresses: mhashemi@iautmu.ac.ir (M. Hashemi), dr.mohsenrashidi@yahoo.com (M. Rashidi), houshmandi.kia7@ut.ac.ir (K. Hushmandi), t.l.m.tenhagen@erasmusmc.nl (T.L.M. ten Hagen), Shokoohmoghadam@yahoo.com (S. Salimimoghadam), a.taheriazam@iautmu.ac.ir (A. Taheriazam), mentezari@iautmu.ac.ir (M. Entezari), m.falahati@erasmusmc.nl (M. Falahati).

https://doi.org/10.1016/j.phrs.2023.106732
Received 25 December 2022; Received in revised form 13 March 2023; Accepted 14 March 2023
Available online 15 March 2023

ARTICLE INFO

Keywords:
HMGA2
Cancer
MiRNA
LncRNA
CircRNAs

ABSTRACT

High mobility group A 2 (HMGA2) is a protein that modulates the structure of chromatin in the nucleus. Importantly, aberrant expression of HMGA2 occurs during carcinogenesis, and this protein is an upstream mediator of cancer hallmarks including evasion of apoptosis, proliferation, invasion, metastasis, and therapy resistance. HMGA2 targets critical signaling pathways such as Wnt/β-catenin and mTOR in cancer cells. Therefore, suppression of HMGA2 function notably decreases cancer progression and improves outcome in patients. As HMGA2 is mainly oncogenic, targeting expression by non-coding RNAs (ncRNAs) is crucial to take into consideration since it affects HMGA2 function. MicroRNAs (miRNAs) belong to ncRNAs and are master regulators of vital cell processes, which affect all aspects of cancer hallmarks. Long ncRNAs (lncRNAs) and circular RNAs (circRNAs), other members of ncRNAs, are upstream mediators of miRNAs. The current review intends to discuss the importance of the miRNA/HMGA2 axis in modulation of various types of cancer, and mentions lncRNAs and circRNAs, which regulate this axis as upstream mediators. Finally, we discuss the effect of miRNAs and HMGA2 interactions on the response of cancer cells to therapy. Regarding the critical role of HMGA2 in regulation of critical signaling pathways in cancer cells, and considering the confirmed interaction between HMGA2 and one of the master regulators of cancer, miRNAs, targeting miRNA/HMGA2 axis in cancer therapy is promising and this could be the subject of future clinical trial experiments.

1. Introduction

The high mobility group (HMG) proteins, identified in 1973, are non-histone components of chromatin, which are placed in only 3% of histone content weight [1–3]. HMG proteins including HMGA, HMGB, and HMGN are involved in modulating chromatin structure and participating in DNA recombination. Importantly, HMG proteins are highly regulated and affected by developmental and environmental factors. Also, aberrant expression of HMGs is shown to change the phenotype of the cell to increase the development of disorders [4–6]. Moreover, chromosomal translocation-induced HMGA gene rearrangement has been detected in benign tumors of mesenchymal origin. Besides, HMGA protein overexpression is a recurrent characteristic of human malignant cancers and is associated with poor prognosis and reduced survival rate in patients. Importantly, several mechanisms are involved in the oncogenic activity of HMGA which includes targeting E2F Transcription Factor 1 (E2F1) and Activator protein 1 (AP1), triggering cyclin A expression, suppression of apoptosis induction by p53, disrupting DNA repair, increasing the expression of inflammatory-related proteins, and targeting factors involved in EMT. It is worth mentioning that HMGA2 is overexpressed during embryogenesis and in cancers, while HMGA2 is hardly detected in normal cells of adults [7]. Regarding this point, targeting HMGA2 for cancer therapy could be a potential strategy in combating cancer.

Non-coding RNAs (ncRNAs) are derived from the non-protein coding part of the genome and a vast number of studies has revealed their critical function in cell processes such as gene expression. NcRNAs are classified based on length: less than 200 nt as microRNAs (miRNAs), and more than 200 nt in length as long non-coding RNAs (lncRNAs) [8–10]. Importantly, ncRNAs are believed to affect all cancer hallmarks and critical signaling pathways in cancer progression which make these molecules eligible for targeting in cancer therapy [11]. Dysregulation of miRNAs has been shown to be associated with malignancies. Also, different characteristics of cancer cells including proliferation, apoptosis, metabolic reprogramming, angiogenesis, metastasis, and therapy resistance have been demonstrated to occur following the alteration in miRNAs expression pattern. MiRNAs mainly have onco-suppressor or oncogenic functions. However, some of them possess both functions. MiRNAs which mediate malignant properties exert their role by suppressing tumor inhibitor genes or upregulating the expression level of oncogenes. In contrast, tumor suppressor miRNAs inhibit cancer progression via attenuation of oncogenes (Table 1). Thus, miRNAs are powerful targets for cancer therapy and use of onco-miRNA inhibitors or synthetic miRNA mimics are two therapeutic approaches. In addition, delivery of miRNAs to the targeted tissue is of importance. Several delivery systems and vectors are developed, including inorganic, polymer-based, and lipid-based vectors, exosomes, and extracellular vesicles [12–14]. More importantly, miRNAs are potential biomarkers for cancer diagnosis and prognosis [15,16], and various clinical trials are in progress to use miRNAs as biomarker tools.

Regarding the critical role of ncRNAs in regulating cancer progression, this review aims to discuss the regulatory role of miRNA on HMGA2 for modulating cancer progression. Moreover, lncRNAs and circular RNAs (circRNAs) as upstream mediators of miRNAs/HMGA2 axis are mentioned in this review. The published articles selected for this review were searched over online web databases and the search was mostly limited to the papers published after 2018.

2. HMGA2 protein

HMGs are non-histone, chromatin-associated proteins, which exert critical functions on DNA processes such as replication, transcription, recombination, and DNA repair. For regulating transcription and maintaining the chromatin structure, HMG proteins bind to the minor

Table 1
The regulatory role of miRNAs in various types of cancer.

Function	Expression level	miRNA	Cancer Type	Signaling network	Ref
Tumor suppressor	Downregulation	miRNA-124–3p	Gastric cancer	HRCT1/ERBB2- MAPK	[17]
		miRNA-944	Tongue cancer	MMP-10/AXL-	[18]
		miRNA-335 and − 145	Breast cancer	PD-L1	[19]
		miRNA-598	Non-small-cell lung cancer (NSCLC)	THBS2	[20]
		miRNA-10a-5p	Clear cell renal cell carcinoma (CCRC)	SERPINE1	[21]
		miRNA-766–3p	Colorectal cancer (CRC)	HNF4G/PI3K/AKT	[22]
		miRNA-4731–5p	Breast cancer	PAICS/FAK	[23]
Tumor promoting	Upregulation	miRNA-375	Prostate cancer	PTPN4/STAT3	[24]
		miRNA-660	Breast cancer	KLHL21/IKKβ/NF-κB/p65	[25]
		miRNA-182	Prostate cancer	MITF	[26]
		miRNA-23b-3p	Salivary adenoid cystic carcinoma	PTEN	[27]
		miRNA-20a	NSCLC	PD-L1	[28]

grooves of DNA. Regarding their non-specificity toward DNA sequences, HMGs supply an excellent mechanism for DNA-protein interaction [29–31]. Three subfamilies exist for the high mobility group of proteins which include HMGA, HMGB, and HMGN, and each one has its "unique protein signature and a functional sequence motif; 'AT-hook' for HMGA, 'HMG-box' for HMGB, and 'Nucleosomal binding domain' for HMGN" [32].

The mammalian high mobility group protein AT-hook (HMGA) consists of "four members including HMGA1a, HMGA1b, and HMGA1c which are encoded by the *HMGA1* gene, and HMGA2 which is encoded by *HMGA2* gene". In addition to the AR-hook domain, which helps to bind short AT enriched sites on DNA, HMGAs also have a C-terminal tail. Interestingly, HMGA1 and HMGA2 have structural and functional similarities, but there are some genes which are targeted only by one of them, resulting in different functions of these two proteins in cancer [4, 32]. In addition to the DNA, HMGA2 could also interact with proteins. For instance, HMGA2 promotes pituitary tumorigenesis by promoting E2F1 activity (Fig. 1) [33,34].

3. Regulatory role of miRNA/HMGA2 axis in gastrointestinal tract cancers

3.1. Gastric cancer

Accumulating data revealed the critical role of HMGA2 in regulation of progression of gastrointestinal cancers. In gastric cancer, it was found that HMGA2 promotes gastric cancer cell motility, growth, EMT, sphere formation, and stem cell induction by augmenting stem cell markers including CD44, Aldehyde dehydrogenase 1 (ALDH1), SRY-box 2 (SOX2), and Oct4, and also EMT-related factors including Snail and β-catenin [35]. EMT is a dynamic and complicated process characterized by losing cell-cell and cell-extracellular adhesion and also gaining mesenchymal properties. Moreover, EMT is a cancer hallmark and is involved in cancer metastasis and invasion processes, as well in drug resistance. EMT is mediated by EMT-related transcription factors including Zinc finger E-box-binding homeobox (ZEB), Zinc finger protein SNAI1 (Snail), TWIST, and Slug [36–38]. It was also found that Twist1, another EMT-related factor, could be regulated by HMGA2 in increasing EMT in gastric cancer [39]. In addition, HMGA2 accelerates transactivation of Forkhead box protein L2 (FOXL2) via E2F1, and FOXL2 downstream target ITGA2 for increasing EMT and metastasis to lymph nodes and distant tissues in gastric cancer [40]. The interaction between miRNAs and HMGA2 for modulating gastric cancer progression has been studied. For instance, miRNA-503 is an onco-suppressor miRNA whose inhibitory role on gastric cancer progression has been confirmed in distinct studies [41,42]. Also, miRNA-503 negatively regulates HMGA2 for its inhibitory function in gastric cancer cells. It was revealed that low expression level of miRNA-503 is associated with poor overall survival, lymph node metastasis, and high tumor size, while its upregulation resulted in inhibition of tumor cell growth, proliferation, colony formation, and invasion [43]. It was shown that miRNA-495 regulates multiple epigenetic modifiers to suppress gastric cancer tumorigenesis [44]. In addition, this miRNA triggers apoptosis and inhibits proliferation and migration in gastric cancer cells via upregulation of caspase 3/9 and Bax, and suppressing Cyclin D1 and PI3K/Akt/-Mammalian target of rapamycin (mTOR) signaling pathway [45]. It bears noting that PI3K/Akt/mTOR is one of the most important signaling pathways in tumorigenesis and has a regulatory role in all of the cancer hallmarks [46,47]. More importantly, invasion and migration of gastric cancer could be suppressed by miRNA-495 through targeting HMGA2 [48]. Another miRNA with inhibitory effect on gastric cancer is miRNA-491. The results of a study have revealed that miRNA-491 attenuates gastric cancer cell proliferation, invasion and migration by targeting JMJD2B [49]. However, suppression of this miRNA by

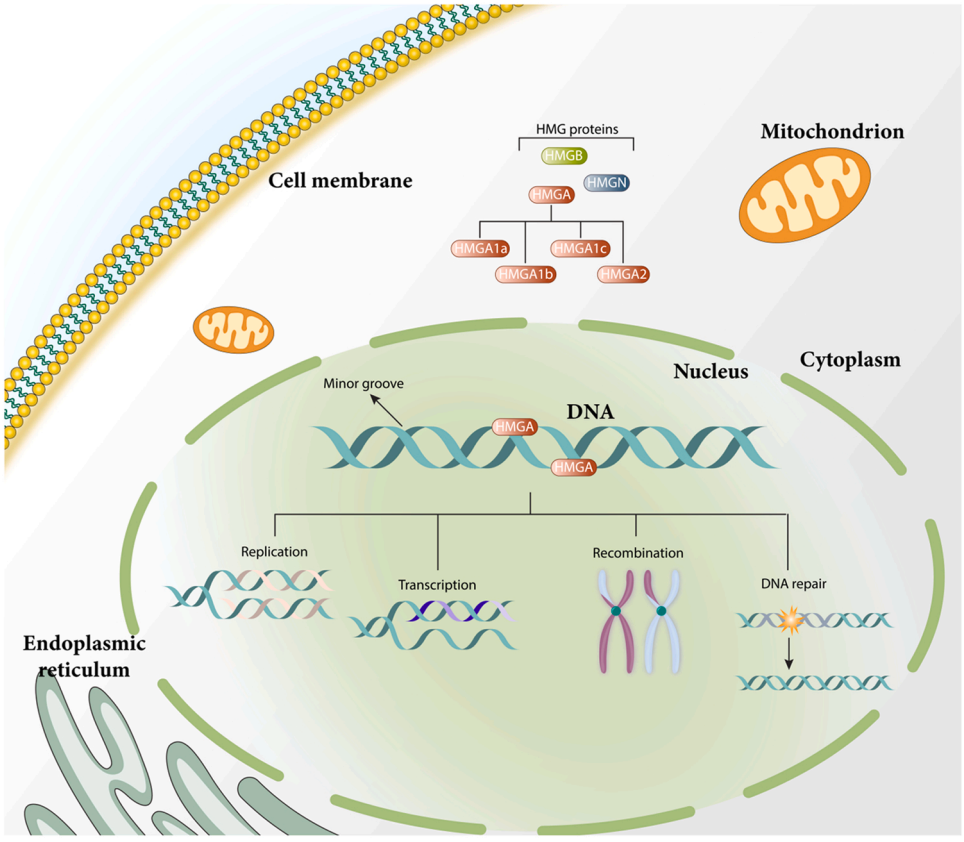

Fig. 1. HMG proteins classification and HMGA functions in cells. HMGA proteins regulate DNA processes including replication, transcription, recombination, and repair by binding to its minor grooves. HMG: High mobility group.

oncogenic factors is in favor of gastric cancer progression. For instance, lncRNA SNHG8 suppresses miRNA-491 to upregulate Platelet Derived Growth Factor Receptor Alpha (PDGFRA) in increasing gastric cancer cell proliferation and invasion [50]. Another study has shown that Forkhead box I1 (Foxi1) binds to the promoter region of miRNA-491–5p to mediate its activation. Then, miRNA-491–5p suppresses the Wnt3a/β-catenin signaling pathway to suppress gastric cancer progression [51]. Wnt/β-catenin signaling exerts critical roles in normal and cancer cells such as regulating homeostasis, development, cell fate, and cancer hallmarks. Wnt/β-catenin high activation in cancers makes it a common target for cancer therapy. However, regarding its important functions in homeostasis, its suppression during cancer therapy is associated with side effects. Interestingly, some cancer-specific Wnt signaling regulators are developed to overcome this issue. Wnt signaling comprises various factors, which regulate its activation or turn off. Briefly, the destruction complex of adenomatous polyposis coli (APC), glycogen synthase kinase-3β (GSK-3β), Axin, and protein phosphatase 2A mediates β-catenin degradation through its phosphorylation and ubiquitination. Upon binding of Wnt ligands to their receptors, the destruction complex is interrupted and then, the level of β-catenin increases in the cytoplasm. After translocation into the nucleus, β-catenin changes the expression level of its downstream targets [52–55]. In addition, it was demonstrated that knock down of miRNA-491 leads to gastric cancer progression. In contrast, miRNA-491 overexpression suppresses cancer proliferation and migration through silencing HMGA2 [56].

MiRNA-490–3p was found to reduce gastric cancer cell proliferation while increasing apoptosis by directly targeting Akt1 [57]. In gastric cancer, circFAM73A upregulation promotes stem cell-like properties of gastric cancer cells to facilitate cell proliferation through regulation of miRNA-490–3p/HMGA2 axis and targeting Heterogeneous nuclear ribonucleoprotein K (HNRNPK) for increasing β-catenin stability. In addition, activity of E2F1 and HNRNPL promotes circFAM73A expression [58]. Circ_0000267 is an oncogenic circRNA with high expression level in hepatocellular carcinoma (HCC) [59]. Also in gastric cancer, circ_0000267 facilitates tumor proliferation, EMT, invasion and metastasis. Circ_0000267 adsorbs miRNA-503–5p to increase HMGA2 expression [60]. Oncogenic function of lncRNA FEZF1-AS1 is revealed in different cancers [61]. For instance, in colorectal cancer lncRNA FEZF1-AS1 promotes tumor proliferation and metastasis [62,63]. Furthermore, Wnt signaling has been shown to be a downstream target of lncRNA FEZF1-AS1 in increasing EMT in NSCLC [64]. Moreover, breast cancer stemness and oncogenesis is regulated by lncRNA FEZF1-AS1 which targets miRNA-30a/Nanog axis [65]. Targeting miRNA-30a by lncRNA FEZF1-AS1 for increasing cancer progression has been also revealed in colorectal cancer [66]. Also, in gastric cancer, lncRNA FEZF1-AS1 targets Wnt signaling to augment tumorigenesis [67]. Interestingly, a study has revealed that lncRNA FEZF1-AS1 which plays oncogenic role in gastric cancer acts as a sponge for miRNA-363–3p to increase HMGA2, thereby promoting gastric cancer stem cell proliferation, invasion, and migration [68]. Similar to lncRNA FEZF1-AS1, various studies have confirmed the oncogenic role of lncRNA OIP5-AS1 in cancers [69–72]. LncRNA OIP5-AS1 promotes gastric cancer cell proliferation while inhibiting apoptosis by increasing HMGA2 function. Furthermore, OIP5-AS1 acts as a sponge for miRNA-367–3p to promote expression of HMGA2 and its downstream targets including PI3K/AKT and Wnt/β-catenin pathways [73]. Additionally, it was elucidated that the expression level of lncRNA ROR and HMGA2 in gastric cancer is increased, while miRNA-519d-3p is downregulated. ROR overexpression leads to promoted cell proliferation,

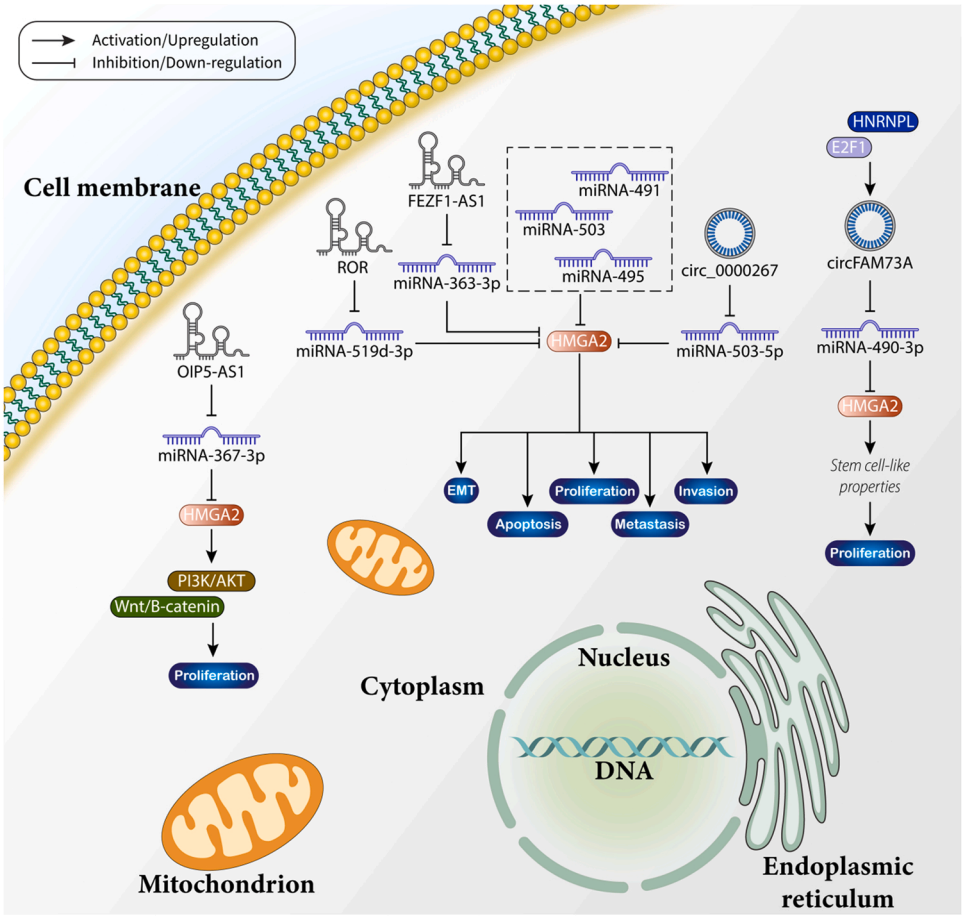

Fig. 2. The miRNA/HMGA2 axis in gastric cancer. MiRNAs with tumor suppressor function in gastric cancer could exert their inhibitory function on cancer progression via inhibiting HMGA2. Tumor promoting lncRNAs and circRNAs augment HMGA2 expression via suppressing these miRNAs to induce cell proliferation, EMT, invasion, and metastasis, and reduce apoptosis in cancer cells through inhibition of miRNAs and upregulation of HMGA2. HMGA2: High mobility group protein AT-hook 2, EMT: Epithelial-to-mesenchymal transition, HNRNPK: Heterogeneous nuclear ribonucleoprotein K, E2F1: Transcription Factor 1, PI3K: Phosphoinositide 3-kinase.

EMT, invasion, and migration. To exert its functions, ROR upregulates HMGA2 via inhibiting miRNA-519d-3p [74]. As lncRNA ROR oncogenic role in different types of tumors including gastric cancer is also proved [75–78], targeting this lncRNA in cancer therapy could be beneficial (Fig. 2).

3.2. Pancreatic cancer

Intriguingly, the critical role of HMGA2 in pancreatic cancer has been studied before. In this study, it was elucidated that HMGA2 is a marker of a subpopulation of pancreatic ductal adenocarcinoma (PDAC) with high metastatic capacity. Furthermore, HMGA2 overexpression was associated with cancer cell growth and metastasis in vivo [79]. A newly discovered lncRNA named HMGA2-AS1 associated with *HMGA2* gene regulates the expression of its own sense gene to mediate tumorigenesis in pancreatic cancer [80]. A lectin-like scavenger receptor named Oxidized Low Density Lipoprotein Receptor 1 (OLR1) upregulates c-Myc expression to increase HMGA2 transcription, thereby augmenting pancreatic cancer cell metastasis. In addition, activation of the OLR1/c-Myc/HMGA2 axis was shown to be associated with worse prognosis compared with patients with a low level of activation of this pathway [81]. In addition, it was found that HMGA2 overexpression in pancreatic cancer is accompanied by increased expression of Snail, ZEB1, N-cadherin and vimentin, while decreased E-cadherin. Moreover, suppression of HMGA2 resulted in inhibited invasion and metastasis [82]. Besides, HMGA2 promotes oncogenesis in pancreatic cancer cells by targeting ANLN [83]. Intriguingly, in vitro and in vivo, miRNA-590 has been shown to suppress cell proliferation and triggers cell apoptosis in PDAC cells via negatively regulating HMGA2 [84]. In addition, miRNA-497 suppresses PDAC cell proliferative and invasive capacity through directly targeting HMGA2 [85]. MiRNA-497 also regulates pancreatic cancer proliferation, migration, and invasion by targeting NF-κB1 [86]. Accumulating evidence has proved anti-tumor activity of miRNA-497 [87–90]. As an example, the critical role of miRNA-497 in inhibiting tumor angiogenesis via targeting Vascular endothelial growth factor receptor 2 (VEGFR2) has been confirmed in a study [91]. In addition, miRNA-497 has been elucidated to be a downstream target of has-circ-0136666 in colorectal cancer. Knocking down of miRNA-497 by these circRNAs leads to activation of PD-L1 and further Treg-mediated immune escape of tumor cells [92]. It was also revealed that miRNA-101 targets Transforming growth factor beta receptor I (TGF-βR1) to suppress oral squamous cell carcinoma (OSCC) [93]. In addition, lncRNA SNHG1 sponges miRNA-101–3p to promote Rho-associated protein kinase (ROCK1) expression in increasing cancer cells proliferation, invasion, and migration [94]. Furthermore, other studies have indicated the importance of miRNA-101 function as an onco-suppressor in cancer [95–97]. In the case of miRNA/HMGA2 interaction, miRNA-101 decreases EMT in pancreatic cancer via negatively affecting HMGA2 [98].

ZFAS1 is a tumor promoting lncRNA whose overexpression in pancreatic cancer results in growth and metastasis of cancer cells. For this purpose, lncRNA ZFAS1 promotes HMGA2 expression via decoying miRNA-497–5p [99]. LncRNA ZFAS1 sponges miRNA-3924 to increase RHOA/ROCK2 and correspondingly augment pancreatic adenocarcinoma metastasis [100]. In addition, stabilization of *HMGCR* mRNA mediated by lncRNA ZFAS1 through binding to U2 auxiliary factor 2 (U2AF2) resulted in pancreatic carcinoma progression [101]. Also, lncRNA CXCR4 inhibits let-7a to promote HMGA2 expression and enhance tumorigenesis and metastasis in pancreatic cancer cells, in vitro and in vivo [102]. Moreover, H19, a well-known oncogenic lncRNA [103–105], suppresses let-7 to increase HMGA2-mediated EMT and metastasis in pancreatic cancer (Fig. 3) [106].

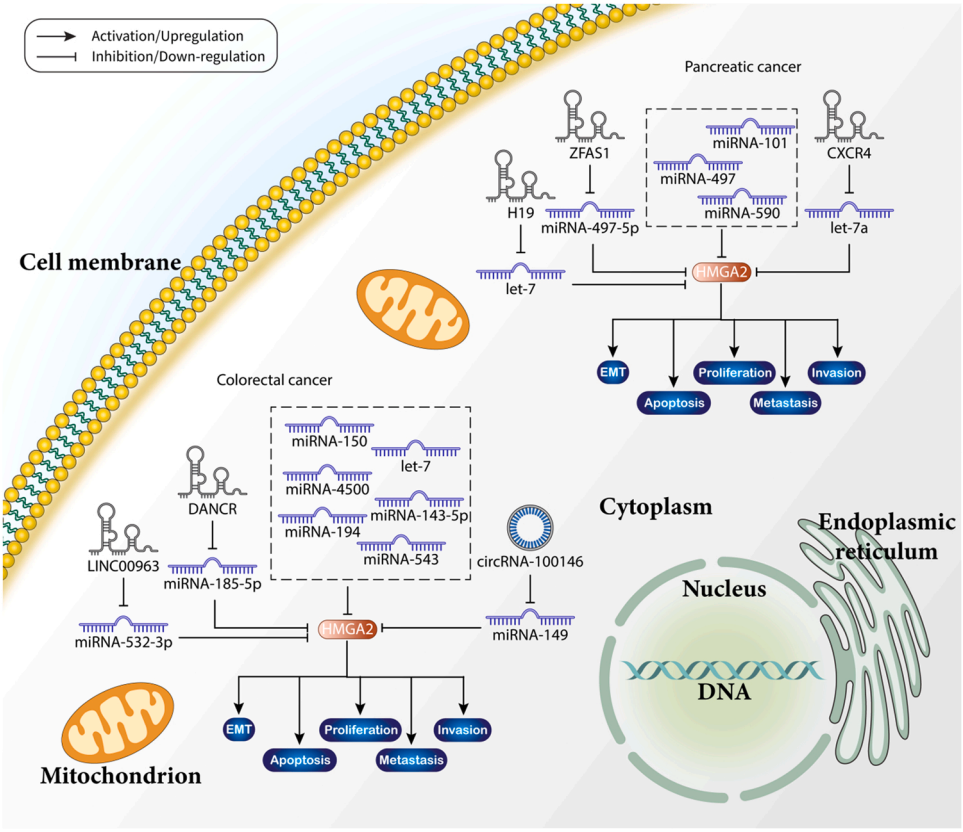

Fig. 3. The miRNA/HMGA2 axis in pancreatic and colorectal cancers. MiRNAs that possess tumor suppressor function in pancreatic and colorectal cancer could exert their function via inhibiting HMGA2. Oncogenic lncRNAs and circRNAs induce cell proliferation, EMT, invasion, and metastasis, and reduce apoptosis in cancer cells through inhibition of miRNAs and upregulation of HMGA2. HMGA2: High mobility group protein AT-hook 2, EMT: Epithelial-to-mesenchymal transition.

3.3. Colorectal cancer

It should be mentioned that the emerging role of HMGA2 in CRC development has been elucidated in various studies [107–110]. As an example, HMGA2 accelerates CRC progression through STAT3-mediated tumor-associated macrophage recruitment [111]. Another study has revealed that HMGA2 overexpression is in favor of resistance to 5-fluorouracil which is mediated by targeting Dvl2/Wnt pathway [112]. Moreover, this oncogene also develops angiogenesis in CRC by targeting both Sema3A and VEGFA [113]. In CRC, it was revealed that miRNA-1249 overexpression inhibits tumor progression and TNM stage, while increasing overall survival. MiRNA-1249 overexpression induced by p53 inhibits tumor growth, proliferation, metastasis and angiogenesis by targeting VEGFA/Akt/mTOR signaling pathway, and suppresses EMT by targeting VEGFA and HMGA2 [114]. In addition, previous studies have confirmed the important role of miRNA-543 in CRC by targeting factors such as PLAS3, large tumor suppressor kinase 1 (LATS1), and PTEN/Akt/mTOR signaling pathway [115–117]. Also, miRNA-543 inhibits CRC cell growth, proliferation, invasion and metastasis by targeting KRAS and Metastasis-associated protein 1 (MTA1), as well HMGA2 [118]. Furthermore, the oncogenic role of HMGA2 in CRC including cell survival and EMT has been elucidated to be suppressed by miRNA-194 [119]. Moreover, miRNA-4500 which negatively regulates HMGA2 expression inhibits CRC cell proliferation, cell cycle progression, invasion and migration [120]. Let-7 has been shown to be downregulated in colon cancer while HMGA2 is increased. It was found that overexpression of let-7 results in HMGA2 suppression, thereby cancer cell proliferation, invasion and metastasis is reduced [121]. MiRNA-150 is also a tumor suppressor agent whose overexpression mediates HMGA2 downregulation and subsequent inhibition of colon cancer cells proliferation and cell cycle progression [122]. Similarly, miRNA-143–5p overexpression in CRC disrupts cancer cell proliferation, EMT, invasion, and metastasis by targeting HMGA2 [123]. Importantly, miRNA-143 has been demonstrated to have a promising role in colorectal cancer therapy [124,125].

It was also found that circRNA-100146 promotes CRC progression via inhibiting miRNA-149 and upregulating HMGA2 [126]. In addition, DANCR is an oncogenic lncRNA whose upregulation is associated with CRC cell proliferation, invasion, cell cycle progression, and metastasis, while decreasing apoptosis. DANCR overexpression is positively correlated with TNM stage and lymph node metastasis. For exerting its function, DANCR suppresses miRNA-185–5p to increase HMGA2 expression [127]. Furthermore, LINC00963 positively affects CRC proliferation, invasion, metastasis, and cell cycle progression by suppressing miRNA-532–3p and upregulation of HMGA2 expression (Fig. 3) [128].

3.4. Esophageal cancer

Like other parts of the gastrointestinal tract, esophageal cancer is also one of the tumors in which HMGA2 expression plays a key role in regulating its progression. It was elucidated that upregulation of HMGA2 by an oncogenic transcriptional co-activator named Hepatitis B virus X-interacting protein (HBXIP) is associated with advanced tumor stage and decreases overall survival in esophageal squamous cell carcinoma (ESCC). Besides, HBXIP increased the phosphorylation of p300/Cyclic adenosine monophosphate Response Element Binding protein Binding Protein (CBP) through Akt pathway to mediate acetylation of HMGA2 at lysine 26, thereby increasing its accumulation, DNA binding capacity and inhibiting its ubiquitination and degradation by proteasomes. Stabilization of HMGA2 ultimately resulted in cancer cell growth in vitro and in vivo [129]. Using RNA sequencing, Wada et al. have revealed that the expression levels of 47 miRNAs, miRNA-143–5p and miRNA-143–3p were decreased in ESCC, while their overexpression inhibited cell proliferation, invasion, and metastasis. It was also demonstrated that miRNA-143–5p targets six genes including *HMGA2*, *Hematological and neurological expressed 1 (HN1)*, *Neuropilin and tolloid-like protein 2 (NETO2)*, *STMN1, Transcription factor 3 (TCF3)*, and Mesenchymal-epithelial transition factor *(MET)* [130].

In ESCC, it was found that miRNA-490–3p upregulation leads to inhibition of HMGA2 reduction and suppression of cancer cell proliferation and metastasis [131]. Moreover, miRNA-125b-5p negatively regulates *HMGA2* at mRNA and protein levels to disrupt proliferation, EMT, invasion, and metastasis in ESCC. It was found that upregulation of miRNA-125–5p not only resulted in reduced level of cell cycle related genes (*CCNA2*, *CCND1*, and *CCNE1*), but also regulates EMT markers including E-cadherin, N-cadherin, Slug, and MMPs [132]. In addition, the oncogenic function of HMGA2 on ESCC cell growth and metastasis has been demonstrated to be suppressed by miRNA-204–5p [133].

In addition, circ-0003340 enhances esophagus cancer tumorigenesis via modulating miRNA-198/HMGA2 axis and this oncogenic axis could be suppressed by dexmedetomidine [134]. Hsa_circ_0006948 directly binds to miRNA-490–3p to sponge it and increase HMGA2 expression in promoting EMT in ESCC [135]. In addition to this circRNA, lncRNAs are also involved in regulating the negative effects of miRNAs on HMGA2 in esophageal cancers. For instance, lncRNA ZEB-AS1 enhanced ESCC proliferation, invasion and metastasis by suppressing miRNA-574–3p and increasing HMGA2 (Fig. 4) [136].

3.5. Tongue cancer

Aggressiveness of tongue squamous cell carcinoma was shown to increase following the HMGA2 upregulation [137]. Moreover, induction of EMT by HMGA2 has been found to be associated with tongue squamous cell carcinoma high metastasis capacity [138]. In tongue squamous cell carcinoma (TSCC), miRNA-493 with onco-suppressor function directly binds HMGA2 to inhibit cancer tumorigenesis, cell proliferation, migration, and invasion, while increasing apoptosis [139].

LncRNA HOTTIP overexpression resulted in a reduction in expression level of miRNA-124–3p and increase in HMGA2 expression. Function of HOTTIP in TSCC ultimately increases tumor proliferation, invasion and migration [140]. Similarly, LINC00466 suppresses TSCC malignant behaviors via rising HMGA2 expression through miRNA-493 suppression [141]. It bears noting that lncRNAs could affect miRNAs through competing endogenous RNA (ceRNA) networks between them which affects cancer progression. For this purpose, lncRNAs compete with miRNAs to regulate the expression level of miRNAs' mRNA targets [142]. For instance, lncRNA H19 knocking down in TSCC impaired cancer cells invasion and metastasis. In TSCC, H19 acts as a ceRNA for let-7a to increase HMGA2, and subsequently EMT, invasion, and metastasis (Fig. 4) [143].

3.6. Hepatocellular cancer

HMGA2 has a crucial role in regulating HCC progression by affecting various cancer hallmarks. For instance, EMT is shown to be induced upon HMGA2 upregulation in HCC [144]. It was demonstrated that EMT is regulated by angiogenin via targeting HMGA2 in HCC [145]. Moreover, propofol has inhibitory effect on HCC cell growth and invasion by suppressing activation of Wnt/β-catenin by HMGA2 [146]. As previously mentioned, miRNAs play onco-suppressor or oncogenic roles in cancer. In HCC, it was found that miRNA-363–3p suppresses carcinogenesis by inhibiting HMGA2 [147]. Also, overexpression of miRNA-760, an upstream regulator of HMGA2, is associated with reduction in HCC progression. Importantly, transcription of miRNA-760 could be suppressed by Specificity protein 1 (SP1), a way by which SP1 promotes HCC progression [148]. Anti-tumor effect of miRNA-9 in HCC is also revealed in a study, and for this purpose, miRNA-9 suppresses HMGA2 [149]. It was found that proliferation and cancer progression in HCC is suppressed by miRNA-377 through targeting HMGA2. In this study, it was uncovered that miRNA-337 inhibits HMGA2 to suppress PI3K/Akt and Wnt/β-catenin pathways in preventing tumor

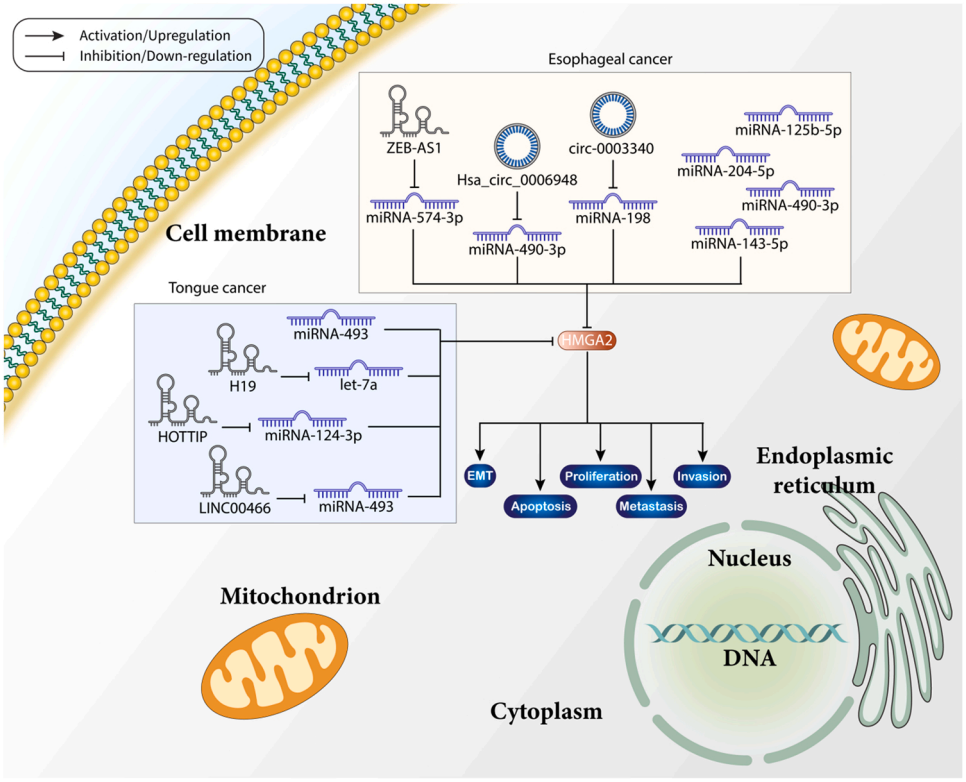

Fig. 4. The miRNA/HMGA2 axis in esophageal and tongue cancers. Onco-suppressor miRNAs inhibits cancer progression by suppressing HMGA2. However, oncogenic lncRNAs and circRNAs attenuate these miRNAs to promote HMGA2 expression, thereby enhancing cell proliferation, EMT, invasion, and metastasis, while decreasing apoptosis. HMGA2: High mobility group protein AT-hook 2, EMT: Epithelial-to-mesenchymal transition.

proliferation and growth, while increasing apoptosis [150]. In addition, it was revealed that the expression level of miRNA-196–5p is decreased following the hypoxic condition in HCC. HMGA2 is a downstream target of miRNA-196–5p whose expression was found to be increased during hypoxia and reduction of miRNA-196–5p [151]. Likewise, miRNA-26a-5p upregulation has been reported as a promising target for HCC therapy. MiRNA-26a-5p inhibits proliferation while promoting apoptosis in HCC and exerts these functions by directly targeting HMGA2 [152]. Similarly, miRNA-663a suppresses HCC proliferation by negatively regulating HMGA2 expression [153].

In HCC, miRNAs which regulate HMGA2 could be also a downstream target of other ncRNAs including circRNAs and lncRNAs. For instance, circZFR promotes HCC progression via downregulation of miRNA-375 and subsequent upregulation of HMGA2 [154]. Likewise, circNFIX upregulation is in favor of HCC cell proliferation and glutaminolysis through inhibiting miRNA-3064–5p and increasing HMGA2 [155]. In addition, LINC00473 serves as ceRNA for miRNA-195 to promote HMGA2 expression, thereby increasing HCC cell progression in vivo and in vitro [156]. Similarly, LINC02476 promotes HCC cell growth by suppressing miRNA-497 and then upregulating HMGA2 [157]. LncRNA EGOT acts in the same way for promoting HCC progression. For this purpose, EGOT enhances HMGA2 expression via suppression of miRNA-33a-5p [158]. CRNDE is a tumor promoting lncRNA with high expression level in HCC. CRNDE upregulates HMGA2 via suppressing miRNA-33a by acting as a ceRNA to promote proliferation and decrease apoptosis in HCC cells [159]. It was demonstrated that lncRNA CCAT1 upregulation is accompanied by HCC progression and proliferation. Besides, overexpression of HMGA2 has been exhibited to be positively associated with tumor associated macrophages (TAMs) markers including CD68, CD163, and CD204. More importantly, upregulation of HMGA2 was associated with TAMs migration capacity. Moreover, it was confirmed that HCC cells progression induced by TAMs is mediated by HMGA2. For this purpose, lncRNA CCAT1 inhibits let-7b to increase HMGA2 [160]. LncRNA HULC acts as a same way to augment HCC cell progression. HULC sequesters miRNA-186 to suppress its inhibitory function on HMGA2, thereby promoting HCC cell growth [161]. LncRNA SNHG16 also serves as a sponge for let-7b-5p to increase HMGA2 expression in enhancing EMT and metastasis in HCC (Fig. 5) [162]. With the attention on the broad activity in gastrointestinal cancers by miRNAs that regulate HMGA2, and regarding the fact that HMGA2 affects most of the cancer hallmarks in these cancer types, using the miRNA/HMGA2 axis seems promising for future gastrointestinal cancer therapy. Also, it should be noted that the downstream targets of HMGA2 in gastrointestinal cancers still remain to be uncovered and further experiments could address this issue.

4. Regulatory role of miRNA/HMGA2 axis in thyroid cancer

HMGA2 overexpression has been also seen in thyroid cancer to be associated with enhanced cancer hallmarks and indicating a prognostic role for HMGA2 [163–166]. Let-7b is a tumor suppressor miRNA whose overexpression in papillary thyroid carcinoma (PTC) is related to inhibited cancer cell invasion and migration. Indeed, let-7b suppresses the expression level of HMGA2 to exert its function [167]. MiRNA-98–5p has been elucidated to be important in inhibiting PTC progression. This miRNA functions as a tumor suppressor through inducing apoptosis and suppressing tumor growth and metastasis by targeting Bax and caspase-3 apoptotic pathways through HMGA2 [168]. Similarly, anti-tumor function of miRNA-143 in PTC has been demonstrated in a study[169]. In this research, authors have shown that miRNA-143 suppressed PTC cell proliferation, invasion and migration by directly targeting HMGA2 [169]. In addition, lncRNA ZFAS1 is overexpressed in PTC and exerts tumor promoting function. It was revealed that ZFAS1 increases HMGA2 expression by acting as a sponge for miRNA-590–3p in promoting tumor cell growth and proliferation [170]. As the number of studies regarding the role of miRNA/HMGA2

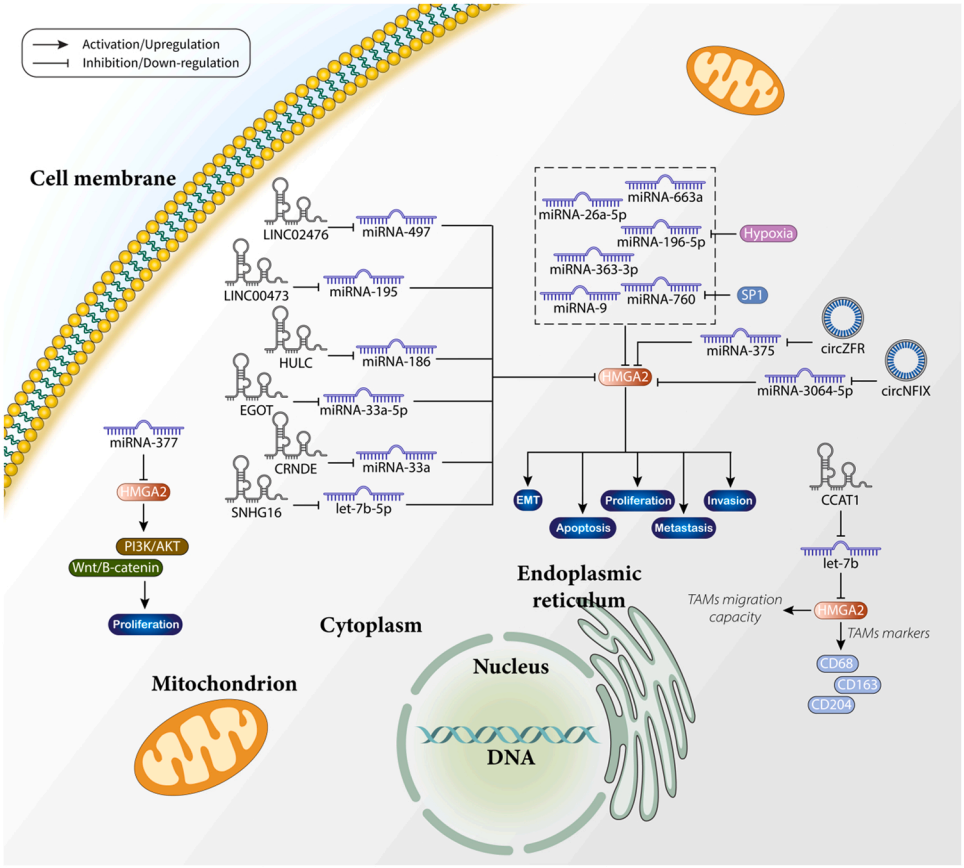

Fig. 5. The miRNA/HMGA2 axis in hepatocellular carcinoma. Onco-suppressor miRNAs negatively regulate HMGA2 in hepatocellular carcinoma. Oncogenic lncRNAs and circRNAs suppress these miRNAs to increase HMGA2 expression, thereby promoting cell proliferation, EMT, invasion, and metastasis, while decreasing apoptosis. HMGA2: High mobility group protein AT-hook 2, SP1: Specificity protein 1, EMT: Epithelial-to-mesenchymal transition, TAMs: tumor associated macrophages, PI3K: Phosphoinositide 3-kinase.

axis in thyroid cancer is low, more in-depth studies could increase the understanding of the critical function of this axis, and leading to find if targeting this pathway could be promising for thyroid cancer therapy.

5. Regulatory role of miRNA/HMGA2 axis in lung cancer

Accumulating data has proved the critical role of HMGA2 in lung cancer [171–173]. For instance, HMGA2 interaction with Protein phosphatase 4 regulatory subunit 1 (PP4R1) resulted in NSCLC metastasis through promoting EMT induced by MAPK/Extracellular signal-regulated kinases (ERK) signaling pathway [174]. Furthermore, although the evidence represents the facts that HMGA2 mainly serves as a downstream factor for ncRNA, some studies have revealed that HMGA2 could target ncRNAs for regulating cancer development. As an example, HMGA2 regulates circRNA ASPH to enhance lung adenocarcinoma cell growth [175]. Moreover, HMGA2 could act as ceRNA for miRNA let-7 to promote NSCLC cell growth, invasion, and dissemination through targeting Transforming growth factor beta receptor type 3 (Tgfbr3)/TGF-β [176]. It bears noting that the interaction between let-7 and HMGA2 in lung cancer has been discussed in several studies [177, 178].

MiRNA-498, a tumor suppressor miRNA, has been confirmed to function in NSCLC as HMGA2 suppressor [179]. MiRNA-219 is another upstream mediator of HMGA2 which regulates cell growth and metastasis [180]. Similarly, miRNA-363–3p directly targets HMGA2 to suppress its oncogenic functions and subsequently inhibits NSCLC growth and invasion [181]. Moreover, in cancer stem cells of NSCLC, miRNA-150–5p acts as a suppressor to inhibit cancer stem cells-induced metastasis and recurrence via targeting Wnt/β-catenin and HMGA2 [182]. MiRNA-154 acts in the same way of aforementioned miRNAs and targets HMGA2 for its further inhibitory function in NSCLC [183]. Also, another study has shown that lung cancer cell proliferation is suppressed via upregulation of miRNA-495 which is an inhibitor of HMGA2 [184]. Additionally, proliferation and invasion of squamous cell carcinoma cells have been elucidated to be suppressed upon miRNA-541 upregulation which inhibits HMGA2 expression [185]. Interestingly, a study has revealed that hydrophobically modified let-7b could be internalized by NSCLC cells, in which let-7b targets HMGA2 for inhibiting cancer progression [186].

In addition, circ-100565 enhances NSCLC proliferation, invasion and migration by increasing HMGA2 through acting as a sponge for miRNA-506–3p [187]. Circ-0000514 overexpression in NSCLC cells is associated with malignancy through suppression of miRNA-330–5p and upregulation of HMGA2 [188]. In NSCLC, it was found that lncRNA VPS9D1 upregulation leads to induction of malignant phenotypes which is exerted by sponging miRNA-532–3p for increasing HMGA2 [189]. Furthermore, lncRNA ZFAS1 downregulation was elucidated to retard NSCLC cells. In contrast, its upregulation is in favor of tumor promotion via inhibiting miRNA-150–5p and increasing HMGA2 (Fig. 6) [190]. These data allowed identifying the critical role of miRNA/HMGA2 axis and its upstream mediator ncRNAs in the regulation of lung cancer progression.

6. Regulatory role of miRNA/HMGA2 axis in breast cancer

Breast cancer cell proliferation, invasion, metastasis [191,192], tumor aggressiveness, and poor prognosis [193] were elucidated as an effect of HMGA2 overexpression in cancer cells. Moreover, Wnt10B/β-catenin signaling is able to induce HMGA2 expression for developing proliferation in metastatic triple negative breast cancer (TNBC) cells [194]. In addition, HMGA2 targets Ten-eleven translocation methylcytosine dioxygenase 1 (TET1)/Homeobox A9 (HOXA9) signaling pathway to promote breast cancer cell growth and metastasis [195]. Also, promoting metastasis of breast cancer cells by HMGA2

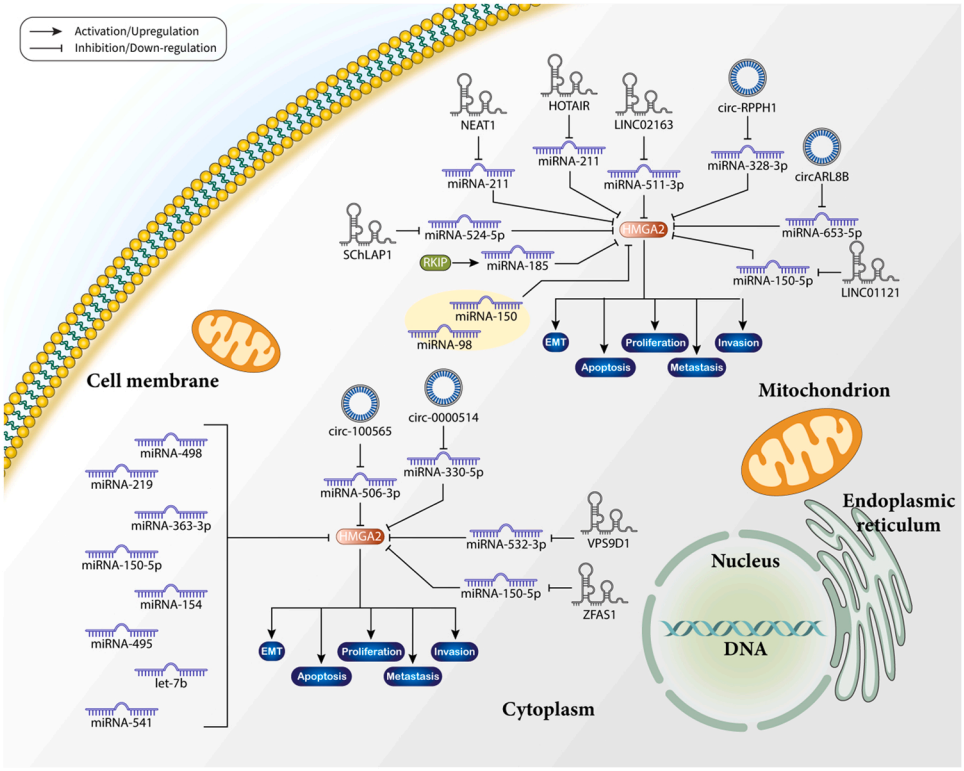

Fig. 6. The miRNA/HMGA2 axis in lung and breast cancer. Various miRNAs have been found to negatively affect HMGA2 in lung and breast cancer. Moreover, lncRNAs and circRNAs with oncogenic function could inhibit these miRNAs to augment HMGA2 expression, thereby promoting cell proliferation, EMT, invasion, and metastasis, and decreasing apoptosis. HMGA2: High mobility group protein AT-hook 2, RKIP: Raf kinase inhibitory protein, EMT: Epithelial-to-mesenchymal transition.

could be exerted by targeting Hippo- Yes-associated protein 1 (YAP) signaling pathway [196]. Intriguingly, it was elucidated that M1 macrophages induced stem cell properties in non-stem breast cancer cells via EMT process in a paracrine manner. In fact, STAT3/NF-κB in macrophages activates Lin-28B-let-7-HMGA2 axis to promote cancer stem cell formation [197].

Accumulating evidence has revealed the critical role of tumor suppressor miRNAs in inhibiting HMGA2 oncogenic functions. For instance, miRNA-150 upregulation in TNBC could be beneficial for suppressing tumor metastasis which is exerted through negative regulation of HMGA2 [198]. Similarly, breast cancer proliferation, invasion and metastasis are all suppressed when HMGA2 expression is reduced by miRNA-98 [199]. Raf kinase inhibitory protein (RKIP) which targets Raf for regulating cell growth and differentiation, has been proven to be involved in regulating miRNAs inhibitory effect on HMGA2. It was elucidated that RKIP increases miRNA-185 to suppress HMGA2 expression, thereby inhibiting breast cancer cell growth and invasion [200].

In addition, circRNAs are one of the upstream mediators of miRNAs and in the case of miRNA/HMGA2 pathway, circRNAs also have regulatory roles. For instance, circRPPH1 overexpression is in favor of cancer progression, while its knock down retards breast cancer tumorigenesis. Circ-RPPH1 acts as a sponge for miRNA-328–3p to promote HMGA2 expression, which is followed by breast cancer cell proliferation, invasion, as well metastasis, while suppressing apoptosis [201]. Furthermore, circARL8B targets miRNA-653–5p/HMGA2 pathway to regulate breast cancer cell progression [202]. Also, LINC02163 facilitates breast cancer malignancy by suppressing miRNA-511–3p and upregulating HMGA2 [203]. In addition, LINC01121 augments breast cancer cell proliferation, invasion and metastasis by targeting miRNA-150–5p/HMGA2 axis [204]. Moreover, HOTAIR is an lncRNA with proven tumor promoting function in breast cancer [205–208]. HOTAIR upregulation accelerates cancer cell progression, and prevents apoptosis induction via suppressing miRNA-20a-5p and increasing HMGA2 expression level [209]. Also, NEAT1 is another common lncRNA with regulatory roles in breast cancer [210–212]. LncRNA NEAT1 prevents negative regulatory function of miRNA-211 on HMGA2 to facilitate cancer cell growth and invasion in breast cancer [213]. Besides, lncRNA SChLAP1 functions in the same way and suppresses miRNA-524–5p to upregulate HMGA2 in increasing TNBC cell proliferation (Fig. 6) [214]. Although these studies have confirmed the importance of miRNAs and HMGA2 interaction in regulation of breast cancer, more in-depth studies may bring a new viewpoint on the crucial function of tumor suppressor miRNAs in the inhibition of breast cancer progression through targeting HMGA2 protein.

7. Regulatory role of miRNA/HMGA2 axis in bladder cancer

HMGA2 affects various aspects of bladder cancer cells including proliferation, invasion, EMT, as well metastasis [215,216]. The critical role of HMGA2 as a prognostic biomarker was confirmed in a study [217,218].

It was demonstrated that let-7c-5p prevents bladder cancer progression via negative regulation HMGA2 [219]. In bladder cancer, circ-0000658 is overexpressed which is in favor of cancer progression. Circ-0000658 exerts its oncogenic function in cancer cells via suppressing miRNA-498 and augmenting HMGA2 expression [220]. It was found that exosomes containing LINC00355 derived from cancer-associated fibroblasts augments bladder cancer cell proliferation and invasion through suppressing miRNA-15a-5p and enhancing HMGA2 expression [221]. As the effect of miRNA/HMGA2 and its upstream regulators on bladder cancer progression is still poorly understood, more detailed studies will reinforce their critical functions in the development of bladder cancer cells.

8. Regulatory role of miRNA/HMGA2 axis in reproductive system cancers

8.1. Ovarian cancer

It is worth noting that overexpression of HMGA2 could be considered as a promising biomarker in high-grade ovarian serous carcinoma [222,

223] and a target for ovarian cancer therapy [224]. In addition, HMGA2 regulates important cancer hallmarks such as proliferation, invasion and metastasis in ovarian cancer [225].

It was demonstrated in a study that dysregulation of miRNA-30c and let-7a leads to HMGA2 overexpression in ovarian cancer, thereby tumor progression. In contrast, upregulation of these miRNAs induced a reverse effect on ovarian cancer progression through HMGA2 suppression [226]. Moreover, it was elucidated that overexpressed miRNA-493–3p leads to apoptosis induction through both intrinsic and extrinsic pathways. MiRNA-493–3p exerts its function via downregulation of mRNA and protein level of *HMGA2*, *AKT2*, *RAF1*, and *ETS1* [227]. Furthermore, miRNA-219–5p downregulation has been shown to be associated with ovarian cancer progression. However, growth and metastasis of cancer cells was diminished followed by miRNA-219–5p upregulation which resulted from HMGA2 reduction by this miRNA (Fig. 7) [228].

8.2. Cervical cancer

In a study, it was demonstrated that HMGA2 overexpression by Estrogen receptor alpha-36 (ER-α36) leads to progression of malignancy in cervical cancer [229]. By affecting Ataxia telangiectasia and Rad3-related protein (ATR)/Checkpoint kinase 1 (Chk1) signaling pathway, HMGA2 promotes EMT and lymph node metastasis in cervical cancer [230]. HMGA2 also promotes the process of cervical intraepithelial neoplasia transition into cervical cancer [231]. Moreover, miRNA-142–3p ectopic expression was found to be accompanied by inhibition of cervical cancer cell growth, migration, and colony formation, while triggering apoptosis. MiRNA-142–3p exerts its onco-suppressor function by targeting not only *HMGA2*, but also other *HMG* genes (Fig. 7) [232].

8.3. Endometrial cancer

Similar to other cancer types, HMGA2 also plays critical roles in endometrial cancer [233]. In endometrial cancer, it was revealed that upregulation of miRNA-302a-5p and miRNA-367–3p is inversely correlated with HMGA2 expression. Overexpression of these two miRNAs is associated with inhibition of lymph node metastasis and malignant behavior of cancer cells which is exerted by suppression of HMGA2 [234]. As an example of regulation of miRNA/HMGA2 axis, circ-0109046 targets miRNA-136 can increase HMGA2 expression for promoting endometrial cancer progression [235]. In addition, lncRNA MIR210HG functions as a sponge for miRNA-337–3p and miRNA-137 to augment HMGA2 expression and promote Wnt/β-catenin and TGF-β/Smad3 signaling pathways in increasing endometrial cancer progression (Fig. 7) [236].

8.4. Prostate cancer

In prostate cancer HMGA2 could repress apoptosis activation and promote invasion and migration of cancer cells. However, knockdown of HMGA2 has opposite effects and leads to activation of apoptotic pathways [237,238]. Activation of EMT occurred in prostate cancer upon overexpression of HMGA2 by targeting MAPK signaling pathway [239]. MiRNA-219–5p has been proven to be an onco-suppressor in prostate cancer by inhibiting HMGA2 to prevent cell growth and metastasis [240]. In prostate cancer, hsa_circ_0062019 has been shown to accelerate cell proliferation, invasion and metastasis via targeting miRNA-195–5p/HMGA2 axis [241]. LncRNA NEAT1 could serve as a sponge for miRNA-98–5p to enhance prostate cancer progression through HMGA2 (Fig. 7) [242]. Although some studies have revealed the critical role of the interaction between miRNAs and HMGA2 in regulating

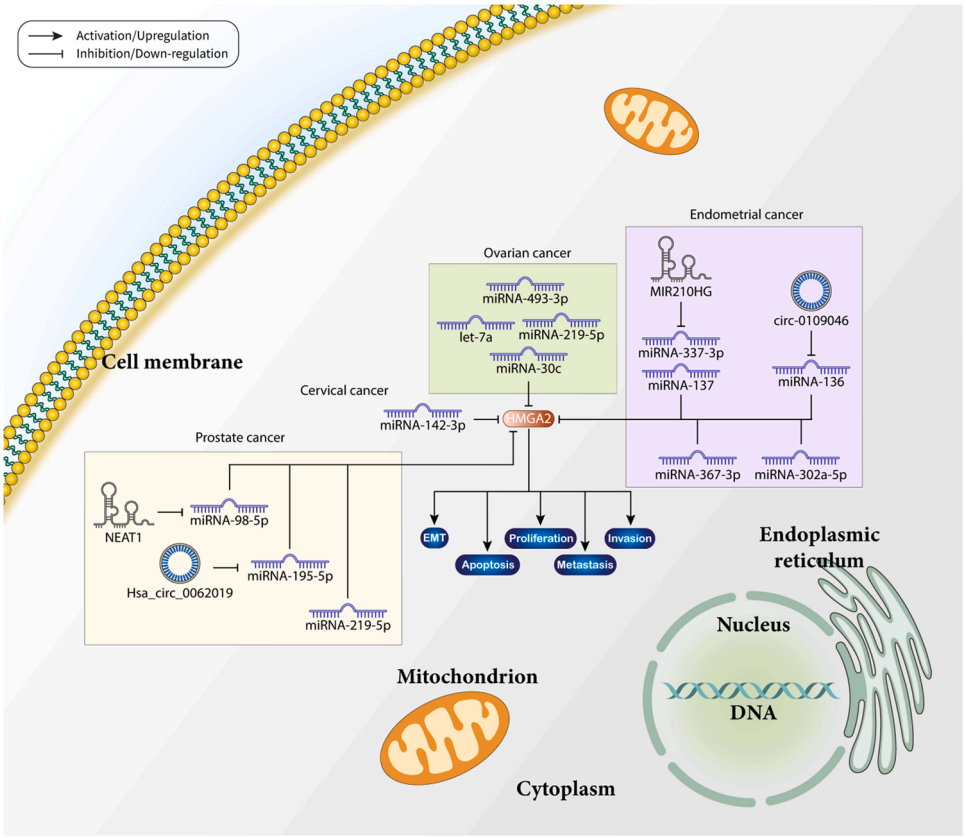

Fig. 7. The miRNA/HMGA2 axis in prostate, cervical, ovarian, and endometrial cancers. MiRNAs reversely affect the expression of HMGA2 to inhibit reproductive system cancer progression. Also, lncRNAs and circRNAs could suppress the inhibitory function of these miRNAs by downregulating their expression, thereby enhancing the tumor progression. HMGA2: High mobility group protein AT-hook, EMT: Epithelial-to-mesenchymal transition.

different hallmarks of reproductive system cancers, also further studies are needed to bring new insight in cancer therapy.

9. Regulatory role of miRNA/HMGA2 axis in brain tumors

In glioblastoma, HMGA2 overexpression is associated with invasion, stemness and tumor formation [243]. Interestingly, the association between HMGA2 polymorphism and brain tumor survival and susceptibility was studied before [244,245]. Besides, it was shown that invasiveness and self-renewal of glioma-initiating cells is increased following the HMGA2 overexpression [246]. HMGA2 was found to augment invasion of glioma cells through activating *MMP2* gene transcription via triggering the chromatin conformational remodeling of the *MMP2* gene promoter [247].

MiRNAs are important molecules with critical function in brain tumors [248,249]. Accumulating data have revealed the importance of miRNA/HMGA2 axis in regulation of brain tumors' progression. For instance, miRNA-370–3p attenuates glioblastoma stem-like cell malignancy and cell growth, invasion, as well metastasis through targeting HMGA2, lncRNA NEAT1, and Hypoxia-inducible factor 1-alpha (HIF1A) [250]. Various studies have revealed the regulatory role of miRNA-370 in glioblastoma. MiRNA-370–3p targets MGMT expression to increase glioblastoma multiforme (GBM) cells sensitivity to temozolomide [251]. Furthermore, miRNA-370–3p directly targets β-catenin to induce cell cycle arrest and suppress cell proliferation in glioma [252]. Despite the importance of miRNA-370–3p in glioblastoma, there wasn't any significant relation between miRNA-370–3p expression and prognosis value for survival. Also, it was demonstrated that temozolomide therapy accompanied by miRNA-370–3p overexpression has better therapeutic effect than temozolomide alone [253]. Similarly, it was demonstrated that glioma cell proliferation and migration are suppressed by miRNA-490–3p due to its inhibitory function on HMGA2 [254]. Moreover, miRNA-340 overexpression was found to suppress glioblastoma multiforme [255]. MiRNA-340–5p downregulation was seen to be correlated with tumor size, recurrence, poor survival, as well density of TAMs and M2-polarized TAMs. On the contrary, overexpression of miRNA-340–5p leads to attenuation of tumor growth and is also associated with good prognosis. For exerting its function, miRNA-340–5p regulates its downstream targets which include Periostin (POSTN), Latent Transforming Growth Factor Beta Binding Protein 1 (LTBP-1), TGFβ-1, and HMGA2. Indeed, miRNA-340–5p- macrophage feedback loop regulates the progression and tumor microenvironment of glioblastoma multiforme [256]. Also, miRNA-211 has been proven to exert onco-suppressor function in GBM [257], and its overexpression resulted in tumor cell growth and EMT suppression mediated by Akt/β-catenin and then HMGA2 suppression [258]. In addition, it seems that miRNA-98 plays critical roles in glioblastoma. For instance, upregulation of miRNA-98 is associated with inhibition of glioma cell invasion via downregulating Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Epsilon (IKKε) [259]. Besides, lncRNA NEAT1 suppresses miRNA-98–5p to upregulate Basic leucine zipper and W2 domain-containing protein 1 (BZW1) in increasing glioma progression [260]. Furthermore, miRNA-98 directly targets PBX3 to attenuate glioma cell invasion and metastasis [261]. Moreover, miRNA-98 exerts the same function and attenuates glioblastoma cell proliferation and invasion by targeting HMGA2 [262].

As an example of the circRNA/miRNA/HMGA2 axis, circABCC1 upregulates HMGA2 by sponging miRNA-591 to promote glioma cell progression [263]. Furthermore, FOXD2-AS1, an oncogenic lncRNA, promotes glioma tumorigenesis and progression by acting as a sponge for miRNA-185–5p to upregulate HMGA2 and further affecting PI3K/Akt signaling pathway [264]. Similarly, LINC00152 inhibits miRNA-107 to increase HMGA2, thereby promoting glioblastoma cell proliferation and invasion [265]. Intriguingly, various studies have indicated activity of LINC00152 in brain tumors as an oncogene. For instance, Wang et al. have suggested a prognostic role for LINC00152 in patients with high-grade glioma [266]. In addition, knocking down of LINC00152 leads to glioblastoma suppression. However, upregulation of LINC00152 leads to sponging miRNA-612, and then augmentation of the AKT2/NF-κB signaling pathway which in turn promotes mesenchymal phenotype-induced glioblastoma malignancy [267]. It bears noting that as miRNA/HMGA2 axis is broadly studied in brain cancer, it could be speculated that use of the miRNAs which inhibits HMGA2 in brain tumors could be a promising miRNA-based therapy and it might be the subject of future investigations.

10. Regulatory role of miRNA/HMGA2 axis in squamous cell carcinoma

In squamous cell carcinoma, increased HMGA2 induces angiogenesis and metastasis to distant tissues and is also associated with poor prognosis [268–270]. Also, in head and neck squamous cell carcinoma (HNSCC) HMGA2 interaction with Snai2 enhances tumorigenesis and stemness [271]. In addition, HMGA2 was elucidated to increase in approximately 90% of ESCC samples and its overexpression is accompanied by malignant phenotype [272]. Also, high expression level of HMGA2 in OSCC cells was associated with decreased recurrence-free survival and was correlated with poor overall survival [273]. Moreover, angiogenin directly regulates HMGA2 overexpression to mediate lung squamous cell carcinoma proliferation, invasion, and metastasis [274]. It was also elucidated that HMGA2 expression is a promising biomarker in UV-induced cutaneous squamous cell carcinoma tumorigenesis [275].

In laryngeal squamous cell carcinoma (LSCC), overexpression of miRNA-98 negatively regulates HMGA2 to suppress EMT. HMGA2 expression is reversely correlated with miRNA-98 and its upregulation increases LSCC cell stem cell-like features. Indeed, HMGA2 regulates POSTN to increase EMT, and miRNA-98 inhibits EMT by suppressing HMGA2/POSTN axis [276]. In addition, it was elucidated that let-7a and HMGA2 expression in LSCC is decreased and increased, respectively, and downregulation of let-7a was shown to be associated with lymph node metastasis, as well high proliferation and invasion. However, overexpression of let-a reverses these cancer hallmarks via down regulating HMGA2 [277].

In HNSCC, tumor cell proliferation, migration and EMT was demonstrated to be suppressed after let-7c overexpression which resulted from HMGA2 downregulation [278]. In addition, hsa_circ_0000264 overexpression has been seen to be accompanied by HNSCC progression. For applying its function, hsa_circ_0000264 acts as a sponge for has-let-7b-5p to increase its downstream target, HMGA2 [279].

Another type of squamous cell carcinoma affects vulva tissue. HMGA2 was found to be critical in genesis and/or progression of vulva tumors [280]. Moreover, aberrant expression of HMGA2 in squamous cell vulvar carcinoma has been revealed to be associated with an aggressive phenotype [281]. Progression of squamous cell carcinoma of vulva could be suppressed by miRNA-30c and let-7a upregulation. These two miRNAs decrease HMGA2 expression, thereby inhibiting cancer progression [282].

11. Regulatory role of miRNA/HMGA2 axis in osteosarcoma

In osteosarcoma, circUBAP2 is a tumor promoting ncRNA whose overexpression is in favor of cancer development [283]. For instance, it promotes osteosarcoma proliferation and invasion by suppressing miRNA-641 and increasing YAP1 [284]. Also, another study has confirmed this oncogenic role for circUBAP2 by targeting miRNA-143 [285]. More importantly, circUBAP2 targets miRNA-204–3p/HMGA2 [286] and miRNA-637/HMGB2 [287] axes to serve its functions. It bears noting that miRNA-204–5p inhibitory role in osteosarcoma was seen to be exerted through targeting EBF2 [288]. In addition, lncRNA CCDC144NL-AS1 promotes HMGA2 by serving as a sponge for miRNA-490–3p to augment proliferation, growth, invasion, and

migration of osteosarcoma cells [289]. Likewise, regulation of miRNA-497–5p/HMGA2 axis by LINC01410 results in increasing the tumorigenesis of osteosarcoma cells [290]. Other studies also have revealed the onco-suppressor function of miRNA-497 in osteosarcoma [291]. MiRNA-497 targets MAPK/ERK in osteosarcoma to suppress cancer progression [292]. In addition, by targeting PI3K/Akt, miRNA-497 inhibits osteosarcoma cell growth and cisplatin resistance [293]. Besides the miRNA-497, LINC01410 also plays a key role in osteosarcoma. For instance, LINC01410 facilitates osteosarcoma cell proliferation and invasion by functioning as a sponge for miRNA-3128 [294]. Also, proliferation and metastasis in osteosarcoma could be also regulated by LINC01410 via targeting miRNA-122–5p/NDRG3 axis [295].

12. Regulatory role of miRNA/HMGA2 axis in other type of cancers

In laryngeal cancer, an interaction between let-7 and HMGA2 was elucidated. It was demonstrated that let-7 inhibits laryngeal cancer progression by negatively regulating HMGA2 [296]. It is of importance to mention that HMGA2, but not HMGA1, is upregulated in larynx carcinoma which highlights the fact that HMGA2 could play a key role in this cancer [297]. In addition, transcriptome profiling has revealed HMGA2 as a biomarker of progression and prognosis in melanoma [298]. MiRNA/HMGA2 axis has also been shown in melanoma. It was proved that let-7a attenuates tumor cell migration by inhibiting HMGA2 expression [299]. In retinoblastoma, a common primary intraocular tumor in children, HMGA2 overexpression was seen to be associated with invasiveness [300]. As mentioned before, miRNA-98 is an onco-suppressor ncRNA which targets HMGA2 in different cancers. Also in retinoblastoma, miRNA-98 suppresses HMGA2 expression to inhibit cancer progression through regulating Wnt/β-catenin [301]. In nasopharyngeal carcinoma, HMGA2 mediates EMT-induced invasion and migration for cancer progression and its overexpression is associated with poor prognosis [302,303]. Furthermore, let-7a suppresses EMT, invasion, and migration of nasopharyngeal carcinoma by targeting HMGA2 [304]. The critical role of miRNA-383–3p in suppressing cell proliferation and radio-resistance in nasopharyngeal carcinoma has been proved in a study through targeting RBM3 [305]. Besides, lncRNA HOXC13 modulates miRNA-383–3p/HMGA2 axis to promote nasopharyngeal carcinoma cell proliferation and invasion [306]. In addition, miRNA-26a directly affects HMGA2 to suppress cell proliferation in gallbladder cancer [307]. In CCRC, miRNA-599 attenuates cancer cell proliferation and invasion by negatively regulating HMGA2 [308]. Also, lncRNA SNHG1 enhances tumor progression via sponging miRNA-103a and increasing HMGA2 in renal cell carcinoma [309].

13. Therapy response

13.1. Regulation of therapy response by miRNAs

Inevitable emergence of resistance to therapy is the major obstacle in cancer therapy. Cancer cells employ different mechanisms to offset therapeutic efficacy of drugs. Due to their plasticity, cancer cells are able to develop resistance to therapies. For this purpose, cancer cells use various mechanisms including [1] alterations in the target through mutations in the drug target or amplification of the target, [2] reactivation of the drug targets via alterations in the upstream or downstream factors of target, [3] activation of other alternative signaling pathways, and [4] the crosstalk between cancer cells and tumor microenvironment (TME) through their adhesive interactions and transmission of signals between them [310]. In addition, TME attenuates drug penetration into tumor cells, preventing clearance of cancer cells by the immune system, promotes proliferation and augments anti-apoptotic pathways to enhance resistance to therapy, without inducing genetic mutations and epigenetic alterations [311,312]. Also, cancer cells inactivate drug, use transporters such as ATP-binding cassette sub-family B member 1 (ABCB1; also known as P-gp) for drug efflux, repair drug-induced DNA damage, and increases epigenetic changes (including DNA methylation, chromatin remodeling, and histone modification) to promote drug resistance. In addition, EMT is one of the cancer hallmarks and drug resistance can also arise following EMT promotion [313–316].

Interestingly, various approaches are in progress to overcome drug resistance in cancer therapy. For instance, it was found that nanotherapeutics could significantly overcome the drug resistance mediated by P-gp for optimal chemotherapy performance [317]. Also, targeting DNA methylation, histone deacetylation, demethylation and methylation is of importance in reversing drug resistance. In addition, combination therapies such as combination of immunotherapy with epigenetics could be efficient in this way [318]. Also, ferroptosis is an iron-dependent cell death that could be targeted for overcoming drug resistance. There are compounds that induce ferroptosis to reverse resistance to immunotherapy and chemotherapeutic drugs [319]. Recently, it was suggested that CRISPR/Cas9 could improve the effectiveness of anti-tumor drugs by targeting critical genes involved in mechanisms of drug resistance. Interestingly, CRISPR/Cas9 is also applicable for detecting drug resistance-related genes and understanding the underlying mechanisms of drug resistance. Also, the CRISPR/-Cas9 system has some limitations in which off-target mutagenesis and anti-SpCas9 antibodies are among them [320].

MiRNAs highly affect therapy response in cancer cells through different mechanisms. For instance, miRNA-17 is highly expressed in CRC. Also, SRY-related HMG box transcription factor 4 (SOX4) upregulates miRNA-17 expression, and miRNA-17 reduces CYLD expression to promote cancer progression and resistance to 5-fluorouracil [321]. Also, it was shown that extracellular vesicles derived from mesenchymal stem cells containing miRNA-301b-3p were able to suppress Thioredoxin interacting protein (TXNIP) in gastric cancer cells to promote drug resistance and tumor cell proliferation and migration [322]. In gemcitabine-resistant bladder cancer cells, miR-99a-5p exert tumor suppressor function by inhibiting SMARCD1 to increase cellular senescence [323]. It was found that miRNA-485–5p overexpression inhibits cell progression and resistance towards cisplatin and carboplatin in OSCC. For this purpose, miRNA-485–5p repressed Keratin 17 (KRT17) which ultimately inhibits integrin β4/α6/FAK/Src/ERK/β-catenin signaling pathway [324]. Table 2 provides more miRNAs with regulatory function on drug resistance.

13.2. MiRNAs delivery to cancer cells

As mentioned previously, use of miRNA mimics or miRNA inhibitors is a promising approach for cancer therapy. However, administration of nucleic acid-based molecules have limitations such as being degraded or removed rapidly from the body, poor cell membrane penetration, unwanted off-target effects, unfavorable pharmacokinetics, and activation of immune response. Thus, application of delivery systems is of importance to minimize the limitations of miRNA-based therapies [343,344]. There are various miRNA delivery systems which include lipid-based nanocarriers (liposome, micelles and nanoemulsion), viral carriers (Adenovirus and retrovirus), and inorganic materials (gold nanoparticles, iron oxide, and quantum dots). In addition, exosomes, apoptotic bodies, platelet-derived microparticles, and microvesicles are cell-derived membranes with capacity for delivering miRNAs [345]. Also, polymer-based carriers are applicable for delivering miRNAs. These polymers are divided into natural and synthetic nanocarriers. Natural polymers could be based on proteins (Albumin, Gelatin, and Atelocollagen), peptides (Cationic peptides and Tachyplesin), and polysaccharides (Chitosan, Cyclodextrin, Dextran, and Hyaluronic acid). Synthetic polymer-based carriers which widely used for delivering therapeutic miRNAs are produced from poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polyethyleneimine (PEI), and poly

Table 2
miRNAs which regulates response to chemotherapeutics in cancer.

Function	miRNA	Cancer	Drug	Mechanism	Ref
Drug sensitivity	miRNA-205	Liver cancer	Doxorubicin	PTEN/PI3K/Akt/P-gp	[325]
	miRNA-199a-3p	TNBC	Cisplatin Veliparib	BRCA1 Suppressing DNA repair Apoptosis induction	[326]
	miRNA-140	Breast cancer	Doxorubicin	FEN1 Suppressing DNA repair	[327]
	miRNA-20a-5p	Ovarian cancer	Cisplatin	DNMT3B)-mediated DNA methylation of RBP1	[328]
	miRNA-146a	Ovarian cancer	Taxane Docetaxel	LAMC2/PI3K/Akt	[329]
	miRNA-5195–3p	TNBC	Paclitaxel	EIF4A2	[330]
	miRNA-552	CRC	5-fluorouracil	SMAD2	[331]
	miRNA-200b and miRNA-200c	Estrogen receptor-positive breast cancer	Tamoxifen	c-MYB	[332]
	miRNA-195	Glioma	Temozolomide	Cyclin E1	[333]
	miRNA-302c	Glioma	Temozolomide	P-gp	[334]
Drug resistance	miRNA-769–5p	Gastric cancer	Cisplatin	Caspase9/caspase3/apoptosis Ubiquitination and degradation of p53	[335]
	miRNA-181b-5p	Breast cancer	Doxorubicin	BCLAF1/p53/p21	[336]
	miRNA-23b/27b/24–1 cluster	CRC	Oxaliplatin	EMT markers (vimentin and SNAI2)	[337]
	miRNA-155–5p	OSCC	5-fluorouracil	TP53INP1	[338]
	miRNA-620	TNBC	Gemcitabine	DCTD	[339]
	miRNA-27a-3p	Glioma	Temozolomide	NF1	[340]
	miRNA-19b	CRC	Oxaliplatin	NR3C1/PI3K/AKT/mTOR	[341]
	miRNA-96–5p	CCRCC	Sunitinib	PTEN	[342]

(ε-caprolactone) (PCL). Moreover, Dendrimers, vehicles with tree-like structures, offer various advantages as they are lipophilic and well-defined, having notable flexibility, their size is adjustable, and their surface could be modified easily (Fig. 8) [346]. Table 3 provides delivery systems which are used for miRNAs delivery to cancers.

13.3. Regulatory role of miRNA/HMGA2 axis in cancer therapy response

In gastric cancer, it was found that exosomal miRNA-107 increases the sensitivity of gastric cancer cells to chemotherapeutic agents by targeting HMGA2 to suppress mTOR/P-glycoprotein (P-gp) pathway [357]. Similarly, miRNA-33b-5p enhances drug sensitivity in gastric cancer cells by suppressing HMGA2 [358]. In addition, lncRNA HCP5 acts as a sponge for miRNA-128 to promote HMGA2 protein in increasing cisplatin resistance in gastric cancer [359]. In CRC, miRNA-204 and miRNA-9–5p overexpression leads to CRC cell sensitivity to 5-fluorouracil via inhibiting HMGA2 expression [360,361]. LncRNA PCAT6 suppresses miRNA-204 by sponging to increase resistance of CRC cells to 5-fluorouracil [362]. In breast cancer, circFBXL5 upregulation was found to be associated with cancer cells resistance to 5-fluorouracil by suppressing miRNA-216b and increasing HMGA2 expression [363]. Also, circTRIM28 augments breast cancer cells resistance to tamoxifen which is exerted by targeting miRNA-409–3p/HMGA2 axis [364]. Also in NSCLC, miRNA-26a overexpression increases the sensitivity of cancer cells to cisplatin via regulating HMGA2-mediated E2F1-Akt pathway [365]. Moreover, miRNA-219–5p suppresses ovarian cancer cells resistance to cisplatin through suppressing HMGA2-induced Wnt/β-catenin and autophagy activation [366]. Furthermore, lncRNA ANRIL attenuates cisplatin sensitivity of ovarian cancer cells via regulating let-7a/HMGA2 axis [367]. In addition, miRNA-34a-5p attenuates glioma cell progression and augments temozolomide-induced cytotoxicity via targeting HMGA2 [368]. Interestingly, it was revealed that a type of herb named Verbascoside promotes the expression level of let-7 g-5p to suppress HMGA2 via Wnt/β-catenin signaling inhibition (Fig. 9) [369]. Although a body of studies has revealed the critical role of miRNA/HMGA2 axis in regulation of hallmarks of cancer progression, few studies have addressed the issue of the capacity of this axis in regulation of therapy response, and investigating this function could bring new insight to the field of cancer therapy.

14. Conclusion and remarks

Cancer therapy is a field in which its challenges are not completely addressed and science increasingly uncovered its gaps and unknown parts. Numerous factors and signaling pathways have been identified and their impact on tumorigenesis established. HMGA2 is a protein belonging to the HMG family of proteins which exerts critical roles in the nucleus. Accumulating evidence has revealed the oncogenic role of HMGA2 in different types of cancers. Interestingly, HMGA2 regulates most of the key oncogenic factors in cells. Also, HMGA2 could be the downstream target of other cancer-related factors which miRNAs are among them. In fact, tumor suppressor miRNAs attenuates HMGA2 expression to inhibit tumor progression. MiRNAs could also be also a downstream target of other ncRNAs including circRNAs and lncRNA. Tumor promoting ncRNAs inhibits miRNAs by acting as a sponge or ceRNA to enhance HMGA2 expression, thereby promoting tumorigenesis and cancer progression. Thus, targeting HMGA2 and suppressing its expression may disrupt further cancer progression and this blocking could result in suppression of cell proliferation, invasion, metastasis, angiogenesis, sensitizing toward therapeutics, or activation of apoptotic pathways. Regarding the critical role of HMGA2 in regulating different cancer hallmarks in many types of cancer, targeting this protein for cancer therapy is of great importance for future studies to study the role of HMGA2 in cancer in more detail and paving the way for clinical studies. Although numerous studies have confirmed the importance of miRNAs/HMGA2 axis, the possible interactions between oncogenic miRNAs and HMGA2 is not evaluated well and future studies could address this issue. Also, another limitation is the lack of supporting data for the oncogenic role of HMGA2. Indeed, as HMGA2 affects the most important cancer hallmarks, further studies should uncover downstream targets of HMGA2 by which it affects cancer progression. In addition, finding these downstream targets could be beneficial in cancer targeted therapy and also might be helpful in reversing therapy resistance in cancer.

Declaration of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Mehrdad Hashemi, Mohsen Rashidi, Kiavash Hushmandi, Timo

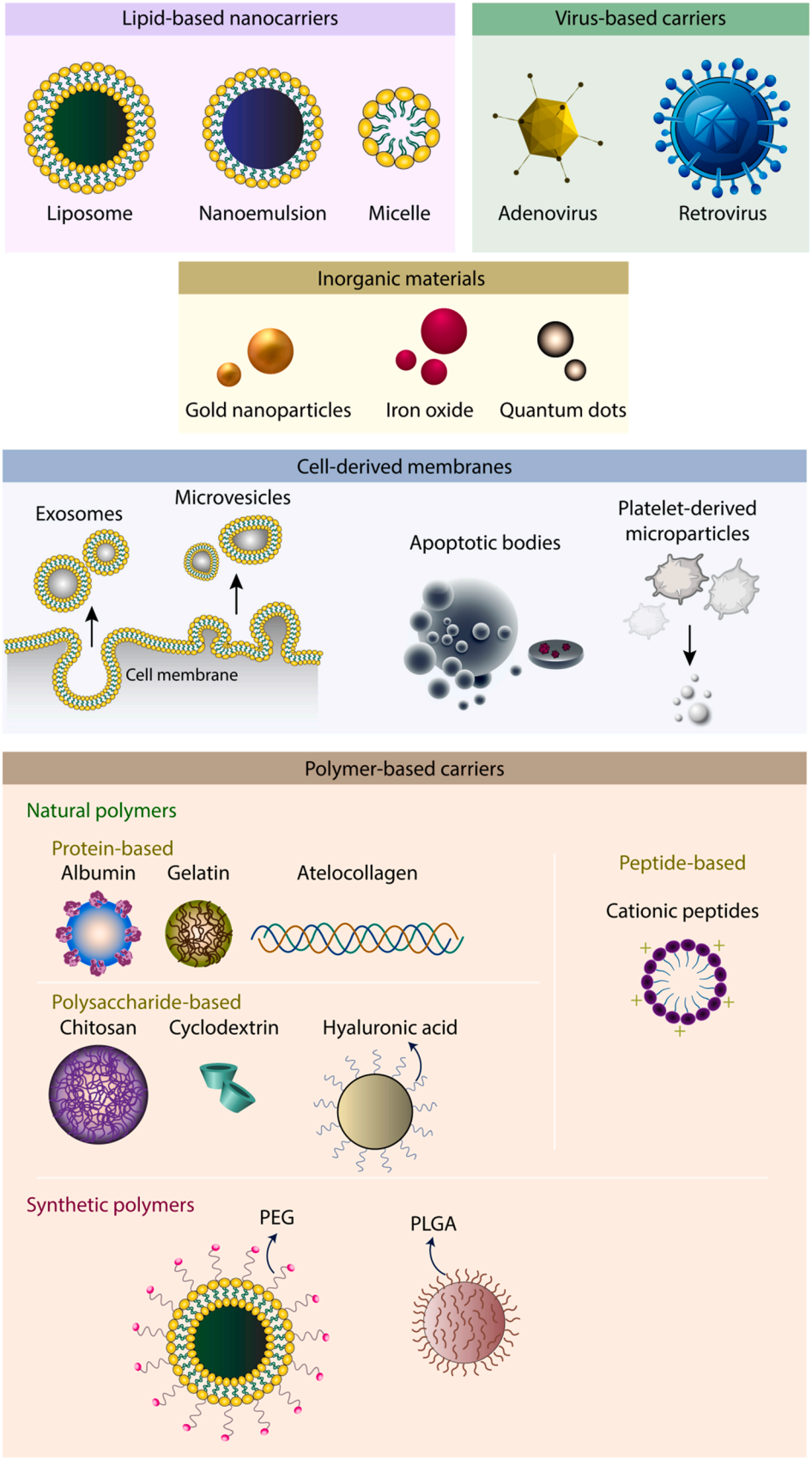

Fig. 8. miRNA delivery systems. A limitation in miRNA-based therapy is that these molecules are degraded in the body quickly and use of a delivery system is of importance to increase miRNAs efficacy in cancer therapy. MiRNAs could be delivered to the target tissue with lipid-based vehicles, carriers which are produced from inorganic materials, cell-derived membranes, and polymer-based vehicles. PLGA: Poly(lactic-co-glycolic acid), PEG: Polyethylene glycol.

Table 3
miRNAs delivery systems in cancer.

miRNA	Cancer type	Delivery system	Target	Affected cancer hallmarks	Ref
miRNA-205	Breast cancer	Dendrimer (Fifth-poly(amidoamine)) functionalized with human luteinizing hormone releasing hormone and acetic anhydride	-	-Cell proliferation	[347]
miRNA-126	Lung cancer	Chitosan decorated with folic acid	Caspase9 ATG5 BECLIN1 EGF-L7	-Migration -Apoptosis -Autophagy -Cell cycle arrest	[348]
miRNA-204	Breast cancer	Exosomes derived from bovine milk coated with hyaluronic acid	Bcl-2 RAB22A	-Cell proliferation	[349]
miRNA-126	NSCLC	Exosomes derived from breast cancer (MDA-MB-231) cells	PTEN/PI3K/AKT	-Cell proliferation -Migration	[350]
miRNA-34a	PDAC	Poly(ethylene glycol)-poly[aspartamidoethyl(p-boronobenzyl) diethylammonium bromide]	c-myc	-Cell proliferation -G2/M phase arrest -Colony formation	[351]
miRNA-9	PDAC	Chimeric peptide supramolecular nanoparticle	eIF5A2	-Apoptosis -Autophagy	[352]
miRNA-124	Androgen-independent prostate cancer cells	PEI-functionalized polyhydroxybutyrate nanoparticles	CPT1A	-Cell proliferation -Motility -Colony formation	[353]
miRNA-34a	TNBC	Layer-by-layer assembled PLGA nanoparticles	CCND-1 Notch-1 Bcl-2 Survivin MDR-1	-Cell proliferation -Cell cycle arrest	[354]
miRNA-320a-3p	Lung cancer	Gold nanorod modified with polyethyleneimine	Sp1/PTEN/MMP9	-Cell proliferation -Metastasis -Apoptosis	[355]
miRNA-660	Lung cancer	Coated Cationic Lipid-nanoparticles	MDM2/p53/p21	-Tumor growth -Cell proliferation	[356]

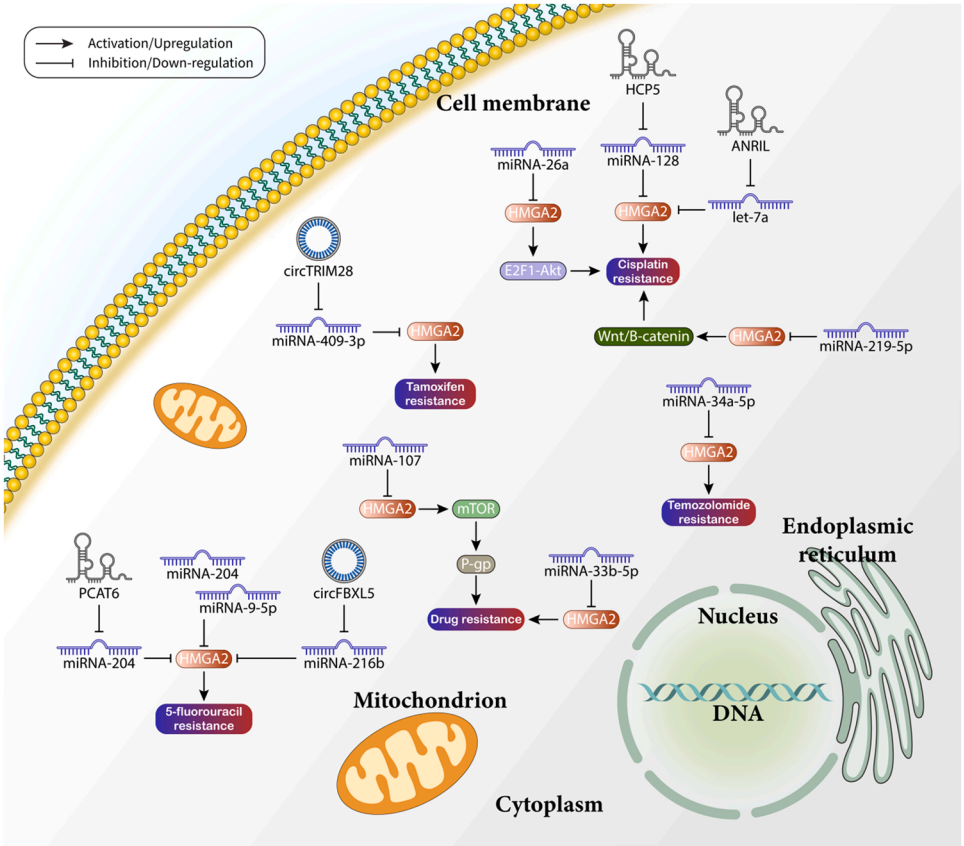

Fig. 9. The miRNA/HMGA2 axis in regulating cancer therapy response. HMGA2 increases drug resistance in cancer directly or through targeting important cellular pathways such as Wnt//β-catenin and mROT, or through transporters involving drug efflux such as P-gp. Furthermore, miRNAs that inhibit HMGA2 to increase drug sensitivity could be downstream targets of other ncRNAs including circRNAs and lncRNAs. HMGA2: High mobility group protein AT-hook 2, mTOR: Mammalian target of rapamycin, E2F1: E2F Transcription Factor 1, P-gp: P-glycoprotein.

L.M.ten Hagen: Conceptualization, Literature survey, Writing – original draft preparation. **Shokooh Salimimoghadam, Afshin Taheriazam, Maliheh Entezari, Mojtaba Falahati**: Supervision, Writing – review & editing.

Declaration of Competing Interest

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript. The following authors have affiliations with organizations with direct or indirect financial interest in the subject matter discussed in the manuscript:

Data availability

No data was used for the research described in the article.

References

[1] M. Bustin, R. Reeves, High-mobility-group chromosomal proteins: architectural components that facilitate chromatin function, Prog. Nucleic Acid. Res. Mol. Biol. 54 (1996) 35–100b.
[2] G.H. Goodwin, C. Sanders, E.W. Johns, A new group of chromatin-associated proteins with a high content of acidic and basic amino acids, Eur. J. Biochem. 38 (1) (1973) 14–19.
[3] N. Ozturk, I. Singh, A. Mehta, T. Braun, G. Barreto, HMGA proteins as modulators of chromatin structure during transcriptional activation, Front. Cell Dev. Biol. 2 (2014) 5.
[4] R. Reeves, Nuclear functions of the HMG proteins, Biochim. Et. Biophys. Acta (BBA)-Gene Regul. Mech. 1799 (1–2) (2010) 3–14.
[5] M. Narita, M. Narita, V. Krizhanovsky, S. Nuñez, A. Chicas, S.A. Hearn, et al., A novel role for high-mobility group a proteins in cellular senescence and heterochromatin formation, Cell 126 (3) (2006) 503–514.
[6] H. Yu, H.H. Lim, N.O. Tjokro, P. Sathiyanathan, S. Natarajan, T.W. Chew, et al., Chaperoning HMGA2 protein protects stalled replication forks in stem and cancer cells, Cell Rep. 6 (4) (2014) 684–697.
[7] A. Fusco, M. Fedele, Roles of HMGA proteins in cancer, Nat. Rev. Cancer 7 (12) (2007) 899–910.
[8] M. Entezari, A. Taheriazam, S. Orouei, S. Fallah, A. Sanaei, E.S. Hejazi, et al., LncRNA-miRNA axis in tumor progression and therapy response: An emphasis on molecular interactions and therapeutic interventions, Biomed. Pharmacother. 154 (2022), 113609.
[9] M. Hashemi, H.Z. Arani, S. Orouei, E. Rostamnejad, A. Ghorbani, M. Khaledabadi, et al., Crosstalk of miRNAs with signaling networks in bladder cancer progression: Therapeutic, diagnostic and prognostic functions, Pharmacol. Res. 185 (2022), 106475.
[10] M. Hashemi, S. Hasani, S. Hajimazdarany, S.R. Mirmazloomi, S. Makvandy, A. Zabihi, et al., Non-coding RNAs targeting notch signaling pathway in cancer: From proliferation to cancer therapy resistance, Int. J. Biol. Macromol. (2022).
[11] M.A. Zandieh, M.H. Farahani, R. Rajabi, K. Karimi, P. Rahmanian, M. Razzazan, et al., Epigenetic regulation of autophagy by non-coding RNAs in gastrointestinal tumors: Biological functions and therapeutic perspectives, Pharmacol. Res. (2022), 106582.
[12] A. Forterre, H. Komuro, S. Aminova, M. Harada, A comprehensive review of cancer MicroRNA therapeutic delivery strategies, Cancers 12 (7) (2020) 1852.
[13] A. Ganju, S. Khan, B.B. Hafeez, S.W. Behrman, M.M. Yallapu, S.C. Chauhan, et al., miRNA nanotherapeutics for cancer, Drug Discov. Today 22 (2) (2017) 424–432.
[14] I. Fernandez-Piñeiro, I. Badiola, A. Sanchez, Nanocarriers for microRNA delivery in cancer medicine, Biotechnol. Adv. 35 (3) (2017) 350–360.
[15] E. Jordan-Alejandre, A.D. Campos-Parra, D.L. Castro-López, M.B. Silva-Cázares, Potential miRNA Use as a Biomarker: From Breast Cancer Diagnosis to Metastasis, Cells 12 (4) (2023) 525.
[16] X. Liang, Q. Wu, Y. Wang, S. Li, MicroRNAs as early diagnostic biomarkers for non-small cell lung cancer, Oncol. Rep. 49 (1) (2023) 1–12.
[17] F. Hou, D.-B. Shi, X.-Y. Guo, R.-N. Zhao, H. Zhang, R.-R. Ma, et al., HRCT1, negatively regulated by miR-124-3p, promotes tumor metastasis and the growth of gastric cancer by activating the ERBB2-MAPK pathway, Gastric Cancer (2023) 1–14.
[18] B. Dharavath, A. Butle, A. Pal, S. Desai, P. Upadhyay, A. Rane, et al., Role of miR-944/MMP10/AXL-axis in lymph node metastasis in tongue cancer. Communications, Biology 6 (1) (2023) 57.
[19] S. Hajibabaei, F. Sotoodehnejadnematalahi, N. Nafissi, S. Zeinali, M. Azizi, Aberrant promoter hypermethylation of miR-335 and miR-145 is involved in breast cancer PD-L1 overexpression, Sci. Rep. 13 (1) (2023) 1003.
[20] X. Li, F. Wu, Mesenchymal stem cell-derived extracellular vesicles transfer miR-598 to inhibit the growth and metastasis of non-small-cell lung cancer by targeting THBS2, Cell Death Discov. 9 (1) (2023) 3.
[21] J. Chang, G. Xiao, W. Zhu, M. Ding, H. Liao, Q. Wang, MicroRNA-10a-5p targets SERPINE1 to suppress cell progression and epithelial–mesenchymal transition process in clear cell renal cell carcinoma, Mol. Cell. Toxicol. (2023) 1–10.
[22] X.-X. He, S.-S. Luo, H.-Q. Qin, X.-W. Mo, MicroRNA-766-3p-mediated downregulation of HNF4G inhibits proliferation in colorectal cancer cells through the PI3K/AKT pathway, Cancer Gene Ther. 29 (6) (2022) 803–813.
[23] L. Lang, J. Tao, C. Yang, W. Li, Tumor suppressive role of microRNA-4731-5p in breast cancer through reduction of PAICS-induced FAK phosphorylation, Cell Death Discov. 8 (1) (2022) 154.
[24] J. Gan, S. Liu, Y. Zhang, L. He, L. Bai, R. Liao, et al., MicroRNA-375 is a therapeutic target for castration-resistant prostate cancer through the PTPN4/STAT3 axis, Exp. Mol. Med. 54 (8) (2022) 1290–1305.
[25] C. Li, R. Li, X. Hu, G. Zhou, G. Jiang, Tumor-promoting mechanisms of macrophage-derived extracellular vesicles-enclosed microRNA-660 in breast cancer progression, Breast Cancer Res. Treat. 192 (2) (2022) 353–368.
[26] M. Stafford, D.J. McKenna, MiR-182 Is Upregulated in Prostate Cancer and Contributes to Tumor Progression by Targeting MITF, Int. J. Mol. Sci. 24 (3) (2023) 1824.
[27] C.-x Hou, N.-n Sun, W. Han, Y. Meng, C.-x Wang, Q.-h Zhu, et al., Exosomal microRNA-23b-3p promotes tumor angiogenesis and metastasis by targeting PTEN in salivary adenoid cystic carcinoma, Carcinogenesis 43 (7) (2022) 682–692.
[28] J. Gong, Y. Shen, F. Jiang, Y. Wang, L. Chu, J. Sun, et al., MicroRNA-20a promotes non-small cell lung cancer proliferation by upregulating PD-L1 by targeting PTEN, Oncol. Lett. 23 (5) (2022) 1–8.
[29] M.R. Rajeswari, A. Jain, High-mobility-group chromosomal proteins, HMGA1 as potential tumour markers, Curr. Sci. (2002) 838–844.
[30] R. Grosschedl, K. Giese, J. Pagel, HMG domain proteins: architectural elements in the assembly of nucleoprotein structures, Trends Genet. 10 (3) (1994) 94–100.
[31] M. Bustin, D.A. Lehn, D. Landsman, Structural features of the HMG chromosomal proteins and their genes, Biochim. Et. Biophys. Acta (BBA)-Gene Struct. Expr. 1049 (3) (1990) 231–243.
[32] S. Zhang, Q. Mo, X. Wang, Oncological role of HMGA2, Int. J. Oncol. 55 (4) (2019) 775–788.
[33] M. Fedele, R. Visone, I. De Martino, G. Troncone, D. Palmieri, S. Battista, et al., HMGA2 induces pituitary tumorigenesis by enhancing E2F1 activity, Cancer Cell 9 (6) (2006) 459–471.
[34] M. Fedele, G.M. Pierantoni, R. Visone, A. Fusco, E2F1 activation is responsible for pituitary adenomas induced by HMGA2 gene overexpression, Cell Div. 1 (1) (2006) 1–5.
[35] J. Sun, B. Sun, D. Zhu, X. Zhao, Y. Zhang, X. Dong, et al., HMGA2 regulates CD44 expression to promote gastric cancer cell motility and sphere formation, Am. J. Cancer Res. 7 (2) (2017) 260.
[36] M. Hashemi, H.Z. Arani, S. Orouei, S. Fallah, A. Ghorbani, M. Khaledabadi, et al., EMT mechanism in breast cancer metastasis and drug resistance: Revisiting molecular interactions and biological functions, Biomed. Pharmacother. 155 (2022), 113774.
[37] M. Hashemi, S. Hajimazdarany, C.D. Mohan, M. Mohammadi, S. Rezaei, Y. Olyaee, et al., Long non-coding RNA/epithelial-mesenchymal transition axis in human cancers: Tumorigenesis, chemoresistance, and radioresistance, Pharmacol. Res. (2022), 106535.
[38] M. Sadrkhanloo, M. Entezari, M. Rashidi, M. Hashemi, R. Raesi, S. Saghari, et al., Non-coding RNAs in EMT regulation: Association with tumor progression and therapy response, Eur. J. Pharmacol. 932 (2022), 175212.
[39] W. Li, Z. Wang, L. Zha, D. Kong, G. Liao, H. Li, HMGA2 regulates epithelial-mesenchymal transition and the acquisition of tumor stem cell properties through TWIST1 in gastric cancer, Oncol. Rep. 37 (1) (2017) 185–192.
[40] J. Dong, R. Wang, G. Ren, X. Li, J. Wang, Y. Sun, et al., HMGA2–FOXL2 Axis Regulates Metastases and Epithelial-to-Mesenchymal Transition of Chemoresistant Gastric CancerHMGA2–FOXL2 Pathway Promotes Metastases and EMT in GC, Clin. Cancer Res. 23 (13) (2017) 3461–3473.
[41] J. Huang, Y.-x Chen, B. Zhang, IGF2-AS affects the prognosis and metastasis of gastric adenocarcinoma via acting as a ceRNA of miR-503 to regulate SHOX2, Gastric Cancer 23 (1) (2020) 23–38.
[42] D. Wu, G. Cao, Z. Huang, K. Jin, H. Hu, J. Yu, et al., Decreased miR-503 expression in gastric cancer is inversely correlated with serum carcinoembryonic antigen and acts as a potential prognostic and diagnostic biomarker, OncoTargets Ther. 10 (2017) 129.
[43] W. Li, J. Li, H. Mu, M. Guo, H. Deng, MiR-503 suppresses cell proliferation and invasion of gastric cancer by targeting HMGA2 and inactivating WNT signaling pathway, Cancer Cell Int. 19 (1) (2019) 1–12.
[44] J.W. Eun, H.S. Kim, Q. Shen, H.D. Yang, S.Y. Kim, J.H. Yoon, et al., MicroRNA-495–3p functions as a tumor suppressor by regulating multiple epigenetic modifiers in gastric carcinogenesis, J. Pathol. 244 (1) (2018) 107–119.
[45] J. Wang, W. Feng, Y. Dong, X. Mao, F. Guo, F. Luo, MicroRNA-495 regulates human gastric cancer cell apoptosis and migration through Akt and mTOR signaling, Oncol. Rep. 40 (6) (2018) 3654–3662.
[46] M.D.A. Paskeh, F. Ghadyani, M. Hashemi, A. Abbaspour, A. Zabolian, S. Javanshir, et al., Biological function and therapeutic perspective of targeting PI3K/Akt signaling in hepatocellular carcinoma: promises and challenges, Pharmacol. Res. (2022), 106553.
[47] M. Hashemi, A. Taheriazam, P. Daneii, A. Hassanpour, S. Rezaei, E.S. Hejazi, et al., Targeting PI3K/Akt signaling in prostate cancer therapy, J. Cell Commun. Signal. (2022) 1–21.
[48] H. Wang, Z. Jiang, H. Chen, X. Wu, J. Xiang, J. Peng, MicroRNA-495 inhibits gastric cancer cell migration and invasion possibly via targeting high mobility group AT-hook 2 (HMGA2), Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 23 (2017) 640.

[49] J. Zhang, J. Ren, S. Hao, F. Ma, Y. Xin, W. Jia, et al., MiRNA-491-5p inhibits cell proliferation, invasion and migration via targeting JMJD2B and serves as a potential biomarker in gastric cancer, Am. J. Transl. Res. 10 (2) (2018) 525.

[50] P. Zhang, S. Li, Z. Chen, Y. Lu, H. Zhang, LncRNA SNHG8 promotes proliferation and invasion of gastric cancer cells by targeting the miR-491/PDGFRA axis, Hum. Cell 33 (1) (2020) 123–130.

[51] R. Sun, Z. Liu, D. Tong, Y. Yang, B. Guo, X. Wang, et al., miR-491-5p, mediated by Foxi1, functions as a tumor suppressor by targeting Wnt3a/β-catenin signaling in the development of gastric cancer, Cell Death Dis. 8 (3) (2017) e2714-e.

[52] M. Hashemi, S. Hasani, S. Hajimazdarany, F. Ghadyani, Y. Olyaee, M. Khodadadi, et al., Biological functions and molecular interactions of Wnt/β-catenin in breast cancer: Revisiting signaling networks, Int. J. Biol. Macromol. (2023), 123377.

[53] Y. Zhang, X. Wang, Targeting the Wnt/β-catenin signaling pathway in cancer, J. Hematol. Oncol. 13 (2020) 1–16.

[54] Y.-S. Jung, J.-I. Park, Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond β-catenin and the destruction complex, Exp. Mol. Med. 52 (2) (2020) 183–191.

[55] Nanotechnology, in silico and endocrine-based strategy for delivering paclitaxel and miRNA: prospects for the therapeutic management of breast cancer, in: M. A. Ansari, M. Thiruvengadam, Z. Farooqui, G. Rajakumar, Q.M.S. Jamal, M. A. Alzohairy, et al. (Eds.), Seminars in cancer biology, 2021.

[56] Z. Liu, Y. Lü, Q. Jiang, Y. Yang, C. Dang, R. Sun, miR-491 inhibits BGC-823 cell migration via targeting HMGA2, Int. J. Biol. Markers 34 (4) (2019) 364–372.

[57] H. Yu, J. Sun, S. Jiang, Y. Xu, MicroRNA-490–3p regulates cell proliferation and apoptosis in gastric cancer via direct targeting of AKT1, Exp. Ther. Med. 17 (2) (2019) 1330–1336.

[58] Y. Xia, J. Lv, T. Jiang, B. Li, Y. Li, Z. He, et al., CircFAM73A promotes the cancer stem cell-like properties of gastric cancer through the miR-490-3p/HMGA2 positive feedback loop and HNRNPK-mediated β-catenin stabilization, J. Exp. Clin. Cancer Res. 40 (1) (2021) 1–24.

[59] H. Pan, L. Tang, H. Jiang, X. Li, R. Wang, J. Gao, et al., Enhanced expression of circ_0000267 in hepatocellular carcinoma indicates poor prognosis and facilitates cell progression by sponging miR-646, J. Cell. Biochem. 120 (7) (2019) 11350–11357.

[60] X. Cai, J. Nie, L. Chen, F. Yu, Circ_0000267 promotes gastric cancer progression via sponging MiR-503–5p and regulating HMGA2 expression, Mol. Genet. Genom. Med. 8 (2) (2020) e1093.

[61] Y. Zhou, S. Xu, H. Xia, Z. Gao, R. Huang, E. Tang, et al., Long noncoding RNA FEZF1-AS1 in human cancers, Clin. Chim. Acta 497 (2019) 20–26.

[62] Z. Bian, J. Zhang, M. Li, Y. Feng, X. Wang, J. Zhang, et al., LncRNA–FEZF1-AS1 Promotes Tumor Proliferation and Metastasis in Colorectal Cancer by Regulating PKM2 SignalingOncogenic Function of FEZF1-AS1 in Colorectal Cancer, Clin. Cancer Res. 24 (19) (2018) 4808–4819.

[63] N. Chen, D. Guo, Q. Xu, M. Yang, D. Wang, M. Peng, et al., Long non-coding RNA FEZF1-AS1 facilitates cell proliferation and migration in colorectal carcinoma, Oncotarget 7 (10) (2016) 11271.

[64] R. He, hu Zhang F, Shen N. LncRNA FEZF1-AS1 enhances epithelial-mesenchymal transition (EMT) through suppressing E-cadherin and regulating WNT pathway in non-small cell lung cancer (NSCLC), Biomed. Pharmacother. 95 (2017) 331–338.

[65] Z. Zhang, L. Sun, Y. Zhang, G. Lu, Y. Li, Z. Wei, Long non-coding RNA FEZF1–AS1 promotes breast cancer stemness and tumorigenesis via targeting miR-30a/Nanog axis, J. Cell. Physiol. 233 (11) (2018) 8630–8638.

[66] J. Li, L.-m Zhao, C. Zhang, M. Li, B. Gao, X.-h Hu, et al., The lncRNA FEZF1-AS1 promotes the progression of colorectal cancer through regulating OTX1 and targeting miR-30a-5p, Oncol. Res. 28 (1) (2020) 51.

[67] X. Wu, P. Zhang, H. Zhu, S. Li, X. Chen, L. Shi, Long noncoding RNA FEZF1-AS1 indicates a poor prognosis of gastric cancer and promotes tumorigenesis via activation of Wnt signaling pathway, Biomed. Pharmacother. 96 (2017) 1103–1108.

[68] Y. Hui, Y. Yang, D. Li, J. Wang, M. Di, S. Zhang, et al., LncRNA FEZF1-AS1 modulates cancer stem cell properties of human gastric cancer through miR-363-3p/HMGA2, Cell Transplant. 29 (2020), 0963689720925059.

[69] S. Ghafouri-Fard, S. Dashti, M. Farsi, B.M. Hussen, M. Taheri, A review on the role of oncogenic lncRNA OIP5-AS1 in human malignancies, Biomed. Pharmacother. 137 (2021), 111366.

[70] Y. Li, X. Han, H. Feng, J. Han, Long noncoding RNA OIP5-AS1 in cancer, Clin. Chim. Acta 499 (2019) 75–80.

[71] Y. Wang, F. Shi, Y. Xia, H. Zhao, LncRNA OIP5–AS1 predicts poor prognosis and regulates cell proliferation and apoptosis in bladder cancer, J. Cell. Biochem. 120 (5) (2019) 7499–7505.

[72] X. Zhang, D. Li, C. Jia, H. Cai, Z. Lv, B. Wu, METTL14 promotes tumorigenesis by regulating lncRNA OIP5-AS1/miR-98/ADAMTS8 signaling in papillary thyroid cancer, Cell death Dis. 12 (6) (2021) 1–17.

[73] Y. Tao, X. Wan, Q. Fan, Y. Wang, H. Sun, L. Ma, et al., Long non-coding RNA OIP5-AS1 promotes the growth of gastric cancer through the miR-367-3p/HMGA2 axis, Dig. Liver Dis. 52 (7) (2020) 773–779.

[74] Jin W., Zhang H., Li M., Lin S. Long noncoding RNA regulator of reprogramming regulates cell growth, metastasis, and cisplatin resistance in gastric cancer via miR-519d-3p/HMGA2 Axis. Cancer Biotherapy & Radiopharmaceuticals, 2020.

[75] Y. Pan, C. Li, J. Chen, K. Zhang, X. Chu, R. Wang, et al., The emerging roles of long noncoding RNA ROR (lincRNA-ROR) and its possible mechanisms in human cancers, Cell. Physiol. Biochem. 40 (1–2) (2016) 219–229.

[76] S. Wang, W. Chen, H. Yu, Z. Song, Q. Li, X. Shen, et al., lncRNA ROR promotes gastric cancer drug resistance, Cancer Control 27 (1) (2020), 1073274820904694.

[77] S.-H. Wang, M.-D. Zhang, X.-C. Wu, M.-Z. Weng, D. Zhou, Z.-W. Quan, Overexpression of LncRNA-ROR predicts a poor outcome in gallbladder cancer patients and promotes the tumor cells proliferation, migration, and invasion, Tumor Biol. 37 (9) (2016) 12867–12875.

[78] H. Li, X. Jiang, X. Niu, Long non-coding RNA reprogramming (ROR) promotes cell proliferation in colorectal cancer via affecting P53, Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 23 (919) (2017).

[79] S.-H. Chiou, M. Dorsch, E. Kusch, S. Naranjo, M.M. Kozak, A.C. Koong, et al., Hmga2 is dispensable for pancreatic cancer development, metastasis, and therapy resistance, Sci. Rep. 8 (1) (2018) 1–10.

[80] G. Ros, S. Pegoraro, P. De Angelis, R. Sgarra, S. Zucchelli, S. Gustincich, et al., HMGA2 antisense long non-coding RNAs as new players in the regulation of HMGA2 expression and pancreatic cancer promotion, Front. Oncol. 9 (2020) 1526.

[81] G. Yang, G. Xiong, M. Feng, F. Zhao, J. Qiu, Y. Liu, et al., OLR1 Promotes Pancreatic Cancer Metastasis via Increased c-Myc Expression and Transcription of HMGA2OLR1–c-Myc–HMGA2 Promotes Metastasis in Pancreatic Cancer, Mol. Cancer Res. 18 (5) (2020) 685–697.

[82] J. Gong, Y. Wang, B. Jiang, B. Xu, C. Hu, Impact of high-mobility-group A2 overexpression on epithelial-mesenchymal transition in pancreatic cancer, Cancer Manag. Res. 11 (2019) 4075.

[83] H.-H. Guo, Y.-Z. Wang, Z.-K. Zhang, M.-Z. Li, X.-D. Tian, Y.-M. Yang, High mobility group AT-hook 2 promotes tumorigenicity of pancreatic cancer cells via upregulating ANLN, Exp. Cell Res. 393 (1) (2020), 112088.

[84] Y.-D. Wang, J.-D. Mao, J.-F. Wang, M.-Q. Xu, MiR-590 suppresses proliferation and induces apoptosis in pancreatic cancer by targeting high mobility group A2, Technol. Cancer Res. Treat. 19 (2020), 1533033820928143.

[85] Z. Zhou, C. Xu, Z. Dong, Y. Wang, J. Duan, C. Yan, MiR-497 inhibits cell proliferation and invasion ability by targeting HMGA2 in pancreatic ductal adenocarcinoma, Eur. Rev. Med Pharm. Sci. 24 (1) (2020) 122–129.

[86] Q. Yu, Z. Xiu, Y. Jian, J. Zhou, X. Chen, X. Chen, et al., microRNA-497 prevents pancreatic cancer stem cell gemcitabine resistance, migration, and invasion by directly targeting nuclear factor kappa B 1, Aging (Albany NY) 14 (14) (2022) 5908.

[87] Q. Luo, X. Li, Y. Gao, Y. Long, L. Chen, Y. Huang, et al., MiRNA-497 regulates cell growth and invasion by targeting cyclin E1 in breast cancer, Cancer Cell Int. 13 (1) (2013) 1–8.

[88] Y. Zhang, Z. Zhu, S. Huang, Q. Zhao, C. Huang, Y. Tang, et al., lncRNA XIST regulates proliferation and migration of hepatocellular carcinoma cells by acting as miR-497-5p molecular sponge and targeting PDCD4, Cancer Cell Int. 19 (1) (2019) 1–13.

[89] L. Cheng, Z. Xing, P. Zhang, W. Xu, Long non-coding RNA LINC00662 promotes proliferation and migration of breast cancer cells via regulating the miR-497-5p/EglN2 axis, Acta Biochim. Pol. 67 (2) (2020) 229–237.

[90] K. Chen, Z. Wang, Q.-B. Zong, M.-Y. Zhou, Q.-F. Chen, miR-497-5p-RSPO2 axis inhibits cell growth and metastasis in glioblastoma, J. Cancer 13 (4) (2022) 1241.

[91] Y. Tu, L. Liu, D. Zhao, Y. Liu, X. Ma, Y. Fan, et al., Overexpression of miRNA-497 inhibits tumor angiogenesis by targeting VEGFR2, Sci. Rep. 5 (1) (2015) 1–15.

[92] Y.-J. Xu, J.-M. Zhao, C. Gao, X.-F. Ni, W. Wang, W.-W. Hu, et al., Hsa_circ_0136666 activates Treg-mediated immune escape of colorectal cancer via miR-497/PD-L1 pathway, Cell. Signal. 86 (2021), 110095.

[93] Y. Wang, R.-Z. Jia, S. Diao, J. He, L. Jia, MiRNA-101 targets TGF-βR1 to retard the progression of oral squamous cell carcinoma, Oncol. Res. 28 (2) (2020) 203.

[94] R. Deng, J. Zhang, J. Chen, lncRNA SNHG1 negatively regulates miRNA-101–3p to enhance the expression of ROCK1 and promote cell proliferation, migration and invasion in osteosarcoma, Int. J. Mol. Med. 43 (3) (2019) 1157–1166.

[95] F. Wu, W. Huang, L. Yang, F. Xu, MicroRNA-101-3p regulates gastric cancer cell proliferation, invasion and apoptosis by targeting PIM 1 expression, Cell. Mol. Biol. 65 (7) (2019) 118–122.

[96] Q. Chen, D. Liu, Z. Hu, C. Luo, S.L. Zheng, miRNA-101-5p inhibits the growth and aggressiveness of NSCLC cells through targeting CXCL6, OncoTargets Ther. 12 (2019) 835.

[97] W. Tong, J. Mu, S. Zhang, LINC00346 accelerates the malignant progression of colorectal cancer via competitively binding to miRNA-101-5p/MMP9, Eur. Rev. Med Pharm. Sci. 24 (12) (2020) 6639–6646.

[98] W. Jiang, W. Gu, R. Qiu, S. He, C. Shen, Y. Wu, et al., miRNA-101 suppresses epithelial-to-mesenchymal transition by targeting HMGA2 in pancreatic cancer cells, Anti-Cancer Agents Med. Chem. (Former. Curr. Med. Chem. -Anti-Cancer Agents) 16 (4) (2016) 432–439.

[99] M. Rao, S. Xu, Y. Zhang, Y. Liu, W. Luan, J. Zhou, Long non-coding RNA ZFAS1 promotes pancreatic cancer proliferation and metastasis by sponging miR-497-5p to regulate HMGA2 expression, Cell Death Dis. 12 (10) (2021) 1–9.

[100] J. Liu, Y. Zhu, C. Ge, LncRNA ZFAS1 promotes pancreatic adenocarcinoma metastasis via the RHOA/ROCK2 pathway by sponging miR-3924, Cancer Cell Int. 20 (1) (2020) 1–15.

[101] L. Wang, Y. Ruan, X. Wu, X. Zhou, lncRNA ZFAS1 Promotes HMGCR mRNA Stabilization via Binding U2AF2 to Modulate Pancreatic Carcinoma Lipometabolism, J. Immunol. Res. (2022) 2022.

[102] G. Xiao, X. Wang, Y. Yu, CXCR4/Let-7a axis regulates metastasis and chemoresistance of pancreatic cancer cells through targeting HMGA2, Cell. Physiol. Biochem. 43 (2) (2017) 840–851.

[103] M. Hashemi, M.S. Moosavi, H.M. Abed, M. Dehghani, M. Aalipour, E.A. Heydari, et al., Long non-coding RNA (lncRNA) H19 in human cancer: From proliferation and metastasis to therapy, Pharmacol. Res. 184 (2022), 106418.

[104] J. Liu, G. Wang, J. Zhao, X. Liu, K. Zhang, G. Gong, et al., LncRNA H19 promoted the epithelial to mesenchymal transition and metastasis in gastric cancer via activating Wnt/β-catenin signaling, Dig. Dis. 40 (4) (2022) 436–447.
[105] Zhang R., Zhang X., Zhang W., Cui W., Xiao Y., Liu L., et al. Sohlh2 regulates the stemness and differentiation of colon cancer stem cells by downregulating LncRNA-H19 transcription. Molecular Cancer Research, 2022.
[106] C. Ma, K. Nong, H. Zhu, W. Wang, X. Huang, Z. Yuan, et al., H19 promotes pancreatic cancer metastasis by derepressing let-7's suppression on its target HMGA2-mediated EMT, Tumor Biol. 35 (9) (2014) 9163–9169.
[107] X. Wang, J. Wang, J. Wu, Emerging roles for HMGA2 in colorectal cancer, Transl. Oncol. 14 (1) (2021), 100894.
[108] X. Deng, F. Kong, S. Li, H. Jiang, L. Dong, X. Xu, et al., A KLF4/PiHL/EZH2/HMGA2 regulatory axis and its function in promoting oxaliplatin-resistance of colorectal cancer, Cell Death Dis. 12 (5) (2021) 1–13.
[109] S.W. Leung, C.-J. Chou, T.-C. Huang, P.-M. Yang, An integrated bioinformatics analysis repurposes an antihelminthic drug niclosamide for treating HMGA2-overexpressing human colorectal cancer, Cancers 11 (10) (2019) 1482.
[110] H. Zhou, L. Li, W. Xie, L. Wu, Y. Lin, X. He, TAGLN and High-mobility Group AT-Hook 2 (HMGA2) complex regulates TGF-β-induced colorectal cancer metastasis, OncoTargets Ther. 13 (2020) 10489.
[111] X. Wang, J. Wang, J. Zhao, H. Wang, J. Chen, J. Wu, HMGA2 facilitates colorectal cancer progression via STAT3-mediated tumor-associated macrophage recruitment, Theranostics 12 (2) (2022) 963.
[112] X. Xu, Y. Wang, H. Deng, C. Liu, J. Wu, M. Lai, HMGA2 enhances 5-fluorouracil chemoresistance in colorectal cancer via the Dvl2/Wnt pathway, Oncotarget 9 (11) (2018) 9963.
[113] Wang C., Long Y., Tao M., Ma H., Li Y., Zhou G., et al. HMGA2 Promotes Colorectal Cancer Angiogenesis via Dual Regulation of Sema3A and VEGFA, 2021.
[114] X. Chen, K. Zeng, M. Xu, X. Liu, X. Hu, T. Xu, et al., P53-induced miR-1249 inhibits tumor growth, metastasis, and angiogenesis by targeting VEGFA and HMGA2, Cell Death Dis. 10 (2) (2019) 1–15.
[115] D. Su, X. Li, J. Chen, J. Dou, G. Fang, C. Luo, MiR-543 inhibits proliferation and metastasis of human colorectal cancer cells by targeting PLAS3, Eur. Rev. Med. Pharmacol. Sci. 24 (17) (2020) 8812–8821.
[116] Y. Liang, D. Zhu, L. Zhu, Y. Hou, L. Hou, X. Huang, et al., Dichloroacetate overcomes oxaliplatin chemoresistance in colorectal cancer through the miR-543/PTEN/Akt/mTOR pathway, J. Cancer 10 (24) (2019) 6037.
[117] Y.-Y. Deng, Y.-J. Min, K. Zhou, Q.-S. Yang, M. Peng, Z.-R. Cui, et al., Identification of the tumor-suppressive role of circular RNA-FOXO3 in colorectal cancer via regulation of miR-543/LATS1 axis, Oncol. Rep. 46 (5) (2021) 1–11.
[118] C. Fan, Y. Lin, Y. Mao, Z. Huang, A.Y. Liu, H. Ma, et al., MicroRNA-543 suppresses colorectal cancer growth and metastasis by targeting KRAS, MTA1 and HMGA2, Oncotarget 7 (16) (2016) 21825.
[119] H.-Y. Chang, S.-P. Ye, S.-L. Pan, T.-T. Kuo, B.C. Liu, Y.-L. Chen, et al., Overexpression of miR-194 reverses HMGA2-driven signatures in colorectal cancer, Theranostics 7 (16) (2017) 3889.
[120] F.Y. Yu, Y. Tu, Y. Deng, C. Guo, J. Ning, Y. Zhu, et al., MiR-4500 is epigenetically downregulated in colorectal cancer and functions as a novel tumor suppressor by regulating HMGA2, Cancer Biol. Ther. 17 (11) (2016) 1149–1157.
[121] Z. Chen, J. Liu, MicroRNA-let-7 targets HMGA2 to regulate the proliferation, migration, and invasion of colon cancer cell HCT116, Evid. -Based Complement. Altern. Med.: eCAM (2021) 2021.
[122] Z. Zhang, G. Wang, L. Yin, M. Li, L. Wu, Increasing miR-150 and lowering HMGA2 inhibit proliferation and cycle progression of colon cancer in SW480 cells, Eur. Rev. Med Pharm. Sci. 22 (20) (2018) 6793–6800.
[123] X. Li, H. Zhang, T. Cui, Y. Wu, S. Wang, MiR-143-5p inhibits proliferation, invasion, and epithelial to mesenchymal transition of colorectal cancer cells by downregulation of HMGA2, Trop. J. Pharm. Res. 20 (7) (2021) 1337–1343.
[124] L. Karimi, T. Zeinali, N. Hosseinahli, B. Mansoori, A. Mohammadi, M. Yousefi, et al., miRNA-143 replacement therapy harnesses the proliferation and migration of colorectal cancer cells in vitro, J. Cell. Physiol. 234 (11) (2019) 21359–21368.
[125] J. Chen, M.-B. Wang, The roles of miRNA-143 in colon cancer and therapeutic implications. Transl Gastrointest, Cancer 1 (2) (2012) 169–174.
[126] K. Liu, Y. Mou, X. Shi, T. Liu, Z. Chen, X. Zuo, Circular RNA 100146 promotes colorectal cancer progression by the MicroRNA 149/HMGA2 Axis, Mol. Cell. Biol. 41 (2) (2021) e00445-20.
[127] W. Lu, Z. Huang, J. Wang, H. Liu, Long non-coding RNA DANCR accelerates colorectal cancer progression via regulating the miR-185-5p/HMGA2 axis, J. Biochem. 171 (4) (2022) 389–398.
[128] J. Ye, J. Liu, T. Tang, L. Xin, X. Bao, Y. Yan, LINC00963 affects the development of colorectal cancer via MiR-532-3p/HMGA2 axis, Cancer Cell Int. 21 (1) (2021) 1–19.
[129] Y. Wu, X. Wang, F. Xu, L. Zhang, T. Wang, X. Fu, et al., The regulation of acetylation and stability of HMGA2 via the HBXIP-activated Akt–PCAF pathway in promotion of esophageal squamous cell carcinoma growth, Nucleic Acids Res. 48 (9) (2020) 4858–4876.
[130] M. Wada, Y. Goto, T. Tanaka, R. Okada, S. Moriya, T. Idichi, et al., RNA sequencing-based microRNA expression signature in esophageal squamous cell carcinoma: Oncogenic targets by antitumor miR-143-5p and miR-143-3p regulation, J. Hum. Genet. 65 (11) (2020) 1019–1034.
[131] N. Kang, S. Ge, R. Zhang, Y. Huang, S. Liu, K. Wu, MiR-490-3p inhibited the proliferation and metastasis of esophageal squamous cell carcinoma by targeting HMGA2, Eur. Rev. Med Pharm. Sci. 22 (23) (2018) 8298–8305.
[132] L.-L. Mei, W.-J. Wang, Y.-T. Qiu, X.-F. Xie, J. Bai, Z.-Z. Shi, miR-125b-5p functions as a tumor suppressor gene partially by regulating HMGA2 in esophageal squamous cell carcinoma, PLoS One 12 (10) (2017), e0185636.
[133] H. Zhang, X. Wu, Z. Sui, Z. Ma, L. Gong, B. Meng, et al., High-mobility group AT-hook 2 promotes growth and metastasis and is regulated by miR-204–5p in oesophageal squamous cell carcinoma, Eur. J. Clin. Investig. 51 (8) (2021), e13563.
[134] J. Che, M. Liu, H. Lv, Dexmedetomidine disrupts esophagus cancer tumorigenesis by modulating circ_0003340/miR-198/HMGA2 axis, Anti-Cancer Drugs 33 (5) (2022) 448–458.
[135] Z. Pan, J. Lin, D. Wu, X. He, W. Wang, X. Hu, et al., Hsa_circ_0006948 enhances cancer progression and epithelial-mesenchymal transition through the miR-490-3p/HMGA2 axis in esophageal squamous cell carcinoma, Aging (Albany NY) 11 (24) (2019) 11937.
[136] J. Xu, R. Chen, L. Liu, X. Li, C. Wu, Y. Zhou, et al., LncRNA ZEB2-AS1 promotes the proliferation, migration and invasion of esophageal squamous cell carcinoma cell through miR-574-3p/HMGA2 axis, Eur. Rev. Med Pharm. Sci. 24 (10) (2020) 5391–5403.
[137] H. Zhang, Z. Tang, C. Deng, Y. He, F. Wu, O. Liu, et al., HMGA 2 is associated with the aggressiveness of tongue squamous cell carcinoma, Oral. Dis. 23 (2) (2017) 255–264.
[138] X.-P. Zhao, H. Zhang, J.-Y. Jiao, D.-X. Tang, Wu Y-l, Pan C-B. Overexpression of HMGA2 promotes tongue cancer metastasis through EMT pathway, J. Transl. Med. 14 (1) (2016) 1–11.
[139] D. Jiao, Y. Liu, Z. Tian, microRNA-493 inhibits tongue squamous cell carcinoma oncogenicity via directly targeting HMGA2, OncoTargets Ther. 12 (2019) 6947.
[140] L. Xiong, Y. Tang, J. Tang, Z. Liu, X. Wang, Downregulation of lncRNA HOTTIP suppresses the proliferation, migration, and invasion of oral tongue squamous cell carcinoma by regulation of HMGA2-mediated Wnt/β-catenin pathway, Cancer Biotherapy Radiopharm. 35 (9) (2020) 720–730.
[141] C. Hou, Y. Dong, B. Du, Long non-coding RNA LINC00466 knockdown inhibits tongue squamous cell carcinoma malignancy by targeting microRNA-493/HMGA2, Cancer Manag. Res. 12 (2020) 13071.
[142] D. Seo, D. Kim, Y. Chae, W. Kim, The ceRNA network of lncRNA and miRNA in lung cancer, Genom. Inform. 18 (2020) 4.
[143] N. Kou, S. Liu, X. Li, W. Li, W. Zhong, L. Gui, et al., H19 facilitates tongue squamous cell carcinoma migration and invasion via sponging miR-let-7, Oncol. Res. 27 (2) (2019) 173.
[144] Y. Luo, W. Li, H. Liao, HMGA2 induces epithelial-to-mesenchymal transition in human hepatocellular carcinoma cells, Oncol. Lett. 5 (4) (2013) 1353–1356.
[145] L. Hengjuan, G. Liu, L. Kun, L. Mingqiu, D. Zhang, Angiogenin regulates epithelial-mesenchymal transition of hepatocellular carcinoma through upregulation of HMGA2. Die Pharmazie-An, Int. J. Pharm. Sci. 74 (5) (2019) 301–304.
[146] W. Ou, J. Lv, X. Zou, Y. Yao, J. Wu, J. Yang, et al., Propofol inhibits hepatocellular carcinoma growth and invasion through the HMGA2–mediated Wnt/β-catenin pathway, Exp. Ther. Med. 13 (5) (2017) 2501–2506.
[147] J. Wang, H. Liang, H. Ge, X. Guo, D. Gu, Y. Yuan, MicroRNA-363–3p inhibits hepatocarcinogenesis by targeting HMGA2 and is associated with liver cancer stage, Mol. Med. Rep. 19 (2) (2019) 935–942.
[148] Q. Wang, G. Wang, X. Xu, Z. Chen, miR-760 mediated the proliferation and metastasis of hepatocellular carcinoma cells by regulating HMGA2, Pathol. -Res. Pract. 222 (2021), 153420.
[149] X. Xu, H. Zou, L. Luo, X. Wang, G. Wang, Micro RNA-9 exerts antitumor effects on hepatocellular carcinoma progression by targeting HMGA 2, FEBS Open Bio 9 (10) (2019) 1784–1797.
[150] H. Cui, R. Song, J. Wu, W. Wang, X. Chen, J. Yin, MicroRNA-337 regulates the PI3K/AKT and Wnt/β-catenin signaling pathways to inhibit hepatocellular carcinoma progression by targeting high-mobility group AT-hook 2, Am. J. Cancer Res. 8 (3) (2018) 405.
[151] H. Zheng, F.-r Bi, Y. Yang, Y.-g Hong, J.-s Ni, L. Ma, et al., Downregulation of miR-196-5p induced by hypoxia drives tumorigenesis and metastasis in hepatocellular carcinoma, Horm. Cancer 10 (4) (2019) 177–189.
[152] W.-J. Zhu, Y. Yan, J.-W. Zhang, Y.-D. Tang, B. Han, Effect and mechanism of miR-26a-5p on proliferation and apoptosis of hepatocellular carcinoma cells, Cancer Manag. Res. 12 (2020) 3013.
[153] W. Huang, J. Li, X. Guo, Y. Zhao, X. Yuan, miR-663a inhibits hepatocellular carcinoma cell proliferation and invasion by targeting HMGA2, Biomed. Pharmacother. 81 (2016) 431–438.
[154] R. Xu, S. Yin, M. Zheng, X. Pei, X. Ji, Circular RNA circZFR promotes hepatocellular carcinoma progression by regulating miR-375/HMGA2 axis, Dig. Dis. Sci. 66 (12) (2021) 4361–4373.
[155] E. Xiao, D. Zhang, W. Zhan, H. Yin, L. Ma, J. Wei, et al., circNFIX facilitates hepatocellular carcinoma progression by targeting miR-3064-5p/HMGA2 to enhance glutaminolysis, Am. J. Transl. Res. 13 (8) (2021) 8697.
[156] J. Mo, B. Li, Y. Zhou, Y. Xu, H. Jiang, X. Cheng, et al., LINC00473 promotes hepatocellular carcinoma progression via acting as a ceRNA for microRNA-195 and increasing HMGA2 expression, Biomed. Pharmacother. 120 (2019), 109403.
[157] Y. Duan, M. Zhao, M. Jiang, Z. Li, C. Ni, LINC02476 promotes the malignant phenotype of hepatocellular carcinoma by sponging miR-497 and increasing HMGA2 expression, OncoTargets Ther. 13 (2020) 2701.
[158] S. Wu, H. Ai, K. Zhang, H. Yun, F. Xie, Long non-coding RNA EGOT promotes the malignant phenotypes of hepatocellular carcinoma cells and increases the expression of HMGA2 via down-regulating miR-33a-5p, OncoTargets Ther. 12 (2019) 11623.

[159] S. Han, B. Han, Z. Li, D. Sun, Downregulation of long noncoding RNA CRNDE suppresses drug resistance of liver cancer cells by increasing microRNA-33a expression and decreasing HMGA2 expression, Cell Cycle 18 (19) (2019) 2524–2537.
[160] L. Deng, S. Huang, B. Chen, Y. Tang, F. Huang, D. Li, et al., Tumor-linked macrophages promote HCC development by mediating the CCAT1/Let-7b/HMGA2 signaling pathway, OncoTargets Ther. 13 (2020) 12829.
[161] Y. Wang, F. Chen, M. Zhao, Z. Yang, J. Li, S. Zhang, et al., The long noncoding RNA HULC promotes liver cancer by increasing the expression of the HMGA2 oncogene via sequestration of the microRNA-186, J. Biol. Chem. 292 (37) (2017) 15395–15407.
[162] S. Li, F. Peng, Y. Ning, P. Jiang, J. Peng, X. Ding, et al., SNHG16 as the miRNA let-7b-5p sponge facilitates the G2/M and epithelial-mesenchymal transition by regulating CDC25B and HMGA2 expression in hepatocellular carcinoma, J. Cell. Biochem. 121 (3) (2020) 2543–2558.
[163] G. Belge, A. Meyer, M. Klemke, K. Burchardt, C. Stern, W. Wosniok, et al., Upregulation of HMGA2 in thyroid carcinomas: a novel molecular marker to distinguish between benign and malignant follicular neoplasias, Genes, Chromosomes Cancer 47 (1) (2008) 56–63.
[164] I. Šamija, N. Mateša, S. Kožaj, I. Majstorović, A. Bolanča, Z. Kusić, HMGA2 gene expression in fine-needle aspiration samples of thyroid nodules as a marker for preoperative diagnosis of thyroid cancer, Appl. Immunohistochem. Mol. Morphol. 27 (6) (2019) 471–476.
[165] P.J. Lappinga, N.S. Kip, L. Jin, R.V. Lloyd, M.R. Henry, J. Zhang, et al., HMGA2 gene expression analysis performed on cytologic smears to distinguish benign from malignant thyroid nodules, Cancer Cytopathol. 118 (5) (2010) 287–297.
[166] G. Chiappetta, A. Ferraro, E. Vuttariello, M. Monaco, F. Galdiero, V. De Simone, et al., HMGA2 mRNA expression correlates with the malignant phenotype in human thyroid neoplasias, Eur. J. Cancer 44 (7) (2008) 1015–1021.
[167] H. Li, L. Zhao, Z. Zhang, H. Zhang, C. Ding, Z. Su, Roles of microRNA let-7b in papillary thyroid carcinoma by regulating HMGA2, Tumor Biol. 39 (10) (2017), 1010428317719274.
[168] K. Qiu, Q. Xie, S. Jiang, T. Lin, miR-98–5p promotes apoptosis and inhibits migration and cell growth in papillary thyroid carcinoma through Bax/Caspase-3 by HMGA2, J. Clin. Lab. Anal. 34 (2) (2020), e23044.
[169] C. Ding, T. Shi, G. Wu, J. Man, H. Han, Y. Cui, The anti-cancer role of microRNA-143 in papillary thyroid carcinoma by targeting high mobility group AT-hook 2, Bioengineered 13 (3) (2022) 6629–6640.
[170] H. Tong, X. Zhuang, J. Cai, Y. Ding, Y. Si, H. Zhang, et al., Long noncoding RNA ZFAS1 promotes progression of papillary thyroid carcinoma by sponging miR-590-3p and upregulating HMGA2 expression, OncoTargets Ther. 12 (2019) 7501.
[171] Meyer B., Loeschke S., Schultze A., Weigel T., Sandkamp M., Goldmann T., et al. HMGA2 overexpression in non-small cell lung cancer. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center, 2007;46(7):503–11.
[172] X. Gao, M. Dai, Q. Li, Z. Wang, Y. Lu, Z. Song, HMGA 2 regulates lung cancer proliferation and metastasis, Thorac. Cancer 8 (5) (2017) 501–510.
[173] F. Di Cello, J. Hillion, A. Hristov, L.J. Wood, M. Mukherjee, A. Schuldenfrei, et al., HMGA2 participates in transformation in human lung cancer, Mol. Cancer Res. 6 (5) (2008) 743–750.
[174] B. Wang, L.Y. Pan, N. Kang, X.Y. Shen, PP4R1 interacts with HMGA2 to promote non-small-cell lung cancer migration and metastasis via activating MAPK/ERK-induced epithelial-mesenchymal transition, Mol. Carcinog. 59 (5) (2020) 467–477.
[175] L. Xu, Y. Ma, H. Zhang, Q.-J. Lu, L. Yang, G.-N. Jiang, et al., HMGA2 regulates circular RNA ASPH to promote tumor growth in lung adenocarcinoma, Cell Death Dis. 11 (7) (2020) 1–10.
[176] M.S. Kumar, E. Armenteros-Monterroso, P. East, P. Chakravorty, N. Matthews, M. M. Winslow, et al., HMGA2 functions as a competing endogenous RNA to promote lung cancer progression, Nature 505 (7482) (2014) 212–217.
[177] X. Li, X. Di, S. Cong, Y. Wang, K. Wang, The role of let-7 and HMGA2 in the occurrence and development of lung cancer: a systematic review and meta-analysis, Eur. Rev. Med Pharm. Sci. 22 (23) (2018) 8353–8366.
[178] Y.S. Lee, A. Dutta, The tumor suppressor microRNA let-7 represses the HMGA2 oncogene, Genes Dev. 21 (9) (2007) 1025–1030.
[179] N. Gao, F. Wang, G. Wang, Q. Zhao, Targeting the HMGA2 oncogene by miR-498 inhibits non-small cell lung cancer biological behaviors, Eur. Rev. Med Pharm. Sci. 22 (6) (2018) 1693–1699.
[180] X. Sun, M. Xu, H. Liu, K. Ming, MicroRNA-219 is downregulated in non-small cell lung cancer and inhibits cell growth and metastasis by targeting HMGA2, Mol. Med. Rep. 16 (3) (2017) 3557–3564.
[181] C. Jiang, Y. Cao, T. Lei, Y. Wang, J. Fu, Z. Wang, et al., microRNA-363-3p inhibits cell growth and invasion of non-small cell lung cancer by targeting HMGA2, Mol. Med. Rep. 17 (2) (2018) 2712–2718.
[182] F.-Q. Dai, C.-R. Li, X.-Q. Fan, L. Tan, R.-T. Wang, H. Jin, miR-150-5p inhibits non-small-cell lung cancer metastasis and recurrence by targeting HMGA2 and β-catenin signaling, Mol. Ther. -Nucleic Acids 16 (2019) 675–685.
[183] H. Zhuo, Y. Song, J. Ye, G. Lai, D. Liu, MicroRNA-154 functions as a tumor suppressor and directly targets HMGA2 in human non-small cell lung cancer, Genet Mol. Res 15 (2016) 2.
[184] J. Sun, Y. Qiao, T. Song, H. Wang, MiR-495 suppresses cell proliferation by directly targeting HMGA2 in lung cancer, Mol. Med. Rep. 19 (3) (2019) 1463–1470.
[185] L. Xu, B. Du, Q.J. Lu, X.W. Fan, K. Tang, L. Yang, et al., miR-541 suppresses proliferation and invasion of squamous cell lung carcinoma cell lines via directly targeting high-mobility group AT-hook 2, Cancer Med. 7 (6) (2018) 2581–2591.
[186] M. Segal, A. Biscans, M.-E. Gilles, E. Anastasiadou, R. De Luca, J. Lim, et al., Hydrophobically modified let-7b miRNA enhances biodistribution to NSCLC and downregulates HMGA2 in vivo, Mol. Ther. -Nucleic Acids 19 (2020) 267–277.
[187] L. Li, H. Wei, H. Zhang, F. Xu, G. Che, Circ_100565 promotes proliferation, migration and invasion in non-small cell lung cancer through upregulating HMGA2 via sponging miR-506-3p, Cancer Cell Int. 20 (1) (2020) 1–12.
[188] L. Jia, M. Liu, L. An, H. Wang, X. Wang, Circ_0000514 promotes the malignant biological behaviors of non-small cell lung cancer cells by modulating miR-330-5p and HMGA2, Pathol. -Res. Pract. 235 (2022), 153913.
[189] X. Han, T. Huang, J. Han, Long noncoding RNA VPS9D1-AS1 augments the malignant phenotype of non-small cell lung cancer by sponging microRNA-532-3p and thereby enhancing HMGA2 expression, Aging (Albany NY) 12 (1) (2020) 370.
[190] Z. Zeng, G. Zhao, C. Rao, G. Hua, M. Yang, X. Miao, et al., Knockdown of lncRNA ZFAS1–suppressed non–small cell lung cancer progression via targeting the miR-150–5p/HMGA2 signaling, J. Cell. Biochem. 121 (8–9) (2020) 3814–3824.
[191] B. Mansoori, M.G. Terp, A. Mohammadi, C.B. Pedersen, H.J. Ditzel, B. Baradaran, et al., HMGA2 supports cancer hallmarks in triple-negative breast cancer, Cancers 13 (20) (2021) 5197.
[192] E. Yang, J. Cisowski, N. Nguyen, K. O'callaghan, J. Xu, A. Agarwal, et al., Dysregulated protease activated receptor 1 (PAR1) promotes metastatic phenotype in breast cancer through HMGA2, Oncogene 35 (12) (2016) 1529–1540.
[193] J. Wu, S. Zhang, J. Shan, Z. Hu, X. Liu, L. Chen, et al., Elevated HMGA2 expression is associated with cancer aggressiveness and predicts poor outcome in breast cancer, Cancer Lett. 376 (2) (2016) 284–292.
[194] P. Wend, S. Runke, K. Wend, B. Anchondo, M. Yesayan, M. Jardon, et al., WNT10B/β-catenin signalling induces HMGA2 and proliferation in metastatic triple-negative breast cancer, EMBO Mol. Med. 5 (2) (2013) 264–279.
[195] M. Sun, C.-X. Song, H. Huang, C.A. Frankenberger, D. Sankarasharma, S. Gomes, et al., HMGA2/TET1/HOXA9 signaling pathway regulates breast cancer growth and metastasis, Proc. Natl. Acad. Sci. 110 (24) (2013) 9920–9925.
[196] C. Kolliopoulos, C.-Y. Lin, C.-H. Heldin, A. Moustakas, P. Heldin, Has2 natural antisense RNA and Hmga2 promote Has2 expression during TGFβ-induced EMT in breast cancer, Matrix Biol. 80 (2019) 29–45.
[197] L. Guo, X. Cheng, H. Chen, C. Chen, S. Xie, M. Zhao, et al., Induction of breast cancer stem cells by M1 macrophages through Lin-28B-let-7-HMGA2 axis, Cancer Lett. 452 (2019) 213–225.
[198] W. Tang, P. Xu, H. Wang, Z. Niu, D. Zhu, Q. Lin, et al., MicroRNA-150 suppresses triple-negative breast cancer metastasis through targeting HMGA2, OncoTargets Ther. 11 (2018) 2319.
[199] M.-J. Wang, H. Zhang, J. Li, H.-D. Zhao, microRNA-98 inhibits the proliferation, invasion, migration and promotes apoptosis of breast cancer cells by binding to HMGA2, Biosci. Rep. 38 (2018) 5.
[200] Q. Zou, H. Wu, F. Fu, W. Yi, L. Pei, M. Zhou, RKIP suppresses the proliferation and metastasis of breast cancer cell lines through up-regulation of miR-185 targeting HMGA2, Arch. Biochem. Biophys. 610 (2016) 25–32.
[201] J. Li, Y. Li, H. Cheng, Circ-RPPH1 knockdown retards breast cancer progression via miR-328-3p-mediated suppression of HMGA2, Clin. Breast Cancer 22 (3) (2022) e286–e295.
[202] H. Wu, J. Xu, G. Gong, Y. Zhang, S. Wu, CircARL8B Contributes to the Development of Breast Cancer Via Regulating miR-653-5p/HMGA2 Axis, Biochem. Genet. 59 (6) (2021) 1648–1665.
[203] C. Qin, L. Jin, J. Li, W. Zha, H. Ding, X. Liu, et al., Long noncoding RNA LINC02163 accelerates malignant tumor behaviors in breast cancer by regulating the MicroRNA-511-3p/HMGA2 axis, Oncol. Res. 28 (5) (2020) 483.
[204] Z. Wang, P. Wang, L. Cao, F. Li, S. Duan, G. Yuan, et al., Long intergenic non-coding RNA 01121 promotes breast cancer cell proliferation, migration, and invasion via the miR-150-5p/HMGA2 axis, Cancer Manag. Res. 11 (2019) 10859.
[205] M. Cantile, M. Di Bonito, M. Cerrone, F. Collina, M. De Laurentiis, G. Botti, Long non-coding RNA HOTAIR in breast cancer therapy, Cancers 12 (5) (2020) 1197.
[206] W. He, D. Li, X. Zhang, LncRNA HOTAIR promotes the proliferation and invasion/metastasis of breast cancer cells by targeting the miR-130a-3p/Suv39H1 axis, Biochem. Biophys. Rep. 30 (2022), 101279.
[207] E. Pawłowska, J. Szczepanska, J. Blasiak, The long noncoding RNA HOTAIR in breast cancer: does autophagy play a role? Int. J. Mol. Sci. 18 (11) (2017) 2317.
[208] L. Zhang, X. Song, X. Wang, Y. Xie, Z. Wang, Y. Xu, et al., Circulating DNA of HOTAIR in serum is a novel biomarker for breast cancer, Breast Cancer Res. Treat. 152 (1) (2015) 199–208.
[209] W. Zhao, D. Geng, S. Li, Z. Chen, M. Sun, Lnc RNA HOTAIR influences cell growth, migration, invasion, and apoptosis via the miR-20a-5p/HMGA 2 axis in breast cancer, Cancer Med. 7 (3) (2018) 842–855.
[210] M. Zhang, W. Wu, Z. Wang, X. Wang, lncRNA NEAT1 is closely related with progression of breast cancer via promoting proliferation and EMT, Eur. Rev. Med Pharm. Sci. 21 (5) (2017) 1020–1026.
[211] E. Knutsen, A.L. Harris, M. Perander, Expression and functions of long non-coding RNA NEAT1 and isoforms in breast cancer, Br. J. Cancer 126 (4) (2022) 551–561.
[212] V.Y. Shin, J. Chen, I.W.-Y. Cheuk, M.-T. Siu, C.-W. Ho, X. Wang, et al., Long non-coding RNA NEAT1 confers oncogenic role in triple-negative breast cancer through modulating chemoresistance and cancer stemness, Cell Death Dis. 10 (4) (2019) 1–10.
[213] X. Li, S. Wang, Z. Li, X. Long, Z. Guo, G. Zhang, et al., The lncRNA NEAT1 facilitates cell growth and invasion via the miR-211/HMGA2 axis in breast cancer, Int. J. Biol. Macromol. 105 (2017) 346–353.

[214] X. Bai, S. Zhang, J. Qiao, X. Xing, W. Li, H. Zhang, et al., Long non-coding RNA SChLAP1 regulates the proliferation of triple negative breast cancer cells via the miR-524–5p/HMGA2 axis, Mol. Med. Rep. 23 (6) (2021) 1–10.
[215] Z. Shi, X. Li, D. Wu, R. Tang, R. Chen, S. Xue, et al., Silencing of HMGA2 suppresses cellular proliferation, migration, invasion, and epithelial–mesenchymal transition in bladder cancer, Tumor Biol. 37 (6) (2016) 7515–7523.
[216] X. Ding, Y. Wang, X. Ma, H. Guo, X. Yan, Q. Chi, et al., Expression of HMGA 2 in bladder cancer and its association with epithelial-to-mesenchymal transition, Cell Prolif. 47 (2) (2014) 146–151.
[217] G. Yang, L. Zhang, J. Bo, K. Hou, X. Cai, Y. Chen, et al., Overexpression of HMGA2 in bladder cancer and its association with clinicopathologic features and prognosis: HMGA2 as a prognostic marker of bladder cancer, Eur. J. Surg. Oncol. (EJSO) 37 (3) (2011) 265–271.
[218] Validation of survivin and HMGA2 as biomarkers for cisplatin resistance in bladder cancer, in: U. Krafft, S. Tschirdewahn, J. Hess, N.N. Harke, B. Hadaschik, C. Olah, et al. (Eds.), Urologic Oncology: Seminars and Original Investigations, Elsevier, 2019.
[219] Y. Yao, C. Zhang, Y. Xiong, B. Han, X. Gao, S. Wang, miR-let-7c-5p inhibits invasion and migration of bladder cancer cells by targeting HMGA2, Nan Fang. yi ke da xue xue bao= J. South. Med. Univ. 41 (7) (2021) 1022–1029.
[220] F. Qiu, Q. Liu, Y. Xia, H. Jin, Y. Lin, X. Zhao, Circ_0000658 knockdown inhibits epithelial-mesenchymal transition in bladder cancer via miR-498-induced HMGA2 downregulation, J. Exp. Clin. Cancer Res. 41 (1) (2022) 1–15.
[221] Y. Zhang, G. Luo, S. You, L. Zhang, C. Liang, X. Chen, Exosomal LINC00355 derived from cancer-associated fibroblasts promotes bladder cancer cell proliferation and invasion by regulating miR-15a-5p/HMGA2 axis, Acta Biochim. Et. Biophys. Sin. 53 (6) (2021) 673–682.
[222] A. Mahajan, Z. Liu, L. Gellert, X. Zou, G. Yang, P. Lee, et al., HMGA2: a biomarker significantly overexpressed in high-grade ovarian serous carcinoma, Mod. Pathol. 23 (5) (2010) 673–681.
[223] D. Califano, S. Pignata, N.S. Losito, A. Ottaiano, S. Greggi, V. De Simone, et al., High HMGA2 expression and high body mass index negatively affect the prognosis of patients with ovarian cancer, J. Cell. Physiol. 229 (1) (2014) 53–59.
[224] A. Malek, E. Bakhidze, A. Noske, C. Sers, A. Aigner, R. Schäfer, et al., HMGA2 gene is a promising target for ovarian cancer silencing therapy, Int. J. Cancer 123 (2) (2008) 348–356.
[225] Y.-N. Xi, X.-Y. Xin, H.-M. Ye, Effects of HMGA2 on malignant degree, invasion, metastasis, proliferation and cellular morphology of ovarian cancer cells, Asian Pac. J. Trop. Med. 7 (4) (2014) 289–292.
[226] A. Agostini, M. Brunetti, B. Davidson, C.G. Tropé, S. Heim, I. Panagopoulos, et al., Genomic imbalances are involved in miR-30c and let-7a deregulation in ovarian tumors: implications for HMGA2 expression, Oncotarget 8 (13) (2017) 21554.
[227] M. Kleemann, H. Schneider, K. Unger, J. Bereuther, S. Fischer, P. Sander, et al., Induction of apoptosis in ovarian cancer cells by miR-493-3p directly targeting AKT2, STK38L, HMGA2, ETS1 and E2F5, Cell. Mol. Life Sci. 76 (3) (2019) 539–559.
[228] F. Xing, Z. Song, Y. He, MiR-219-5p inhibits growth and metastasis of ovarian cancer cells by targeting HMGA2, Biol. Res. 51 (1) (2018) 1–7.
[229] C. Wang, T. Zhang, K. Wang, S. Zhang, Q. Sun, X. Yang, ER-α36 promotes the malignant progression of cervical cancer mediated by estrogen via HMGA2, Front. Oncol. (2021) 11.
[230] W.-Y. Wang, Y.-X. Cao, X. Zhou, B. Wei, L. Zhan, L.-T. Fu, HMGA2 gene silencing reduces epithelial-mesenchymal transition and lymph node metastasis in cervical cancer through inhibiting the ATR/Chk1 signaling pathway, Am. J. Transl. Res. 10 (10) (2018) 3036.
[231] L. Wang, H. Shen, D. Zhu, B. Feng, L. Yu, X. Tian, et al., Increased high mobility group A 2 expression promotes transition of cervical intraepithelial neoplasm into cervical cancer, Oncotarget 9 (8) (2018) 7891.
[232] P. Sharma, P. Yadav, D. Karunagaran, Ectopic expression of miR-142-3p suppresses growth, migration, colony formation and induces apoptosis by down-regulating HMGA1, HMGA2, HMGB1 and HMGB3 in human cervical cancer cells, Cancer Res. 80 (16_Supplement) (2020), 2517-.
[233] L. Wei, X. Liu, W. Zhang, Y. Wei, Y. Li, Q. Zhang, et al., Overexpression and oncogenic function of HMGA2 in endometrial serous carcinogenesis, Am. J. Cancer Res. 6 (2) (2016) 249.
[234] J. Ma, D. Li, F.-F. Kong, D. Yang, H. Yang, X.-X. Ma, miR-302a-5p/367-3p-HMGA2 axis regulates malignant processes during endometrial cancer development, J. Exp. Clin. Cancer Res. 37 (1) (2018) 1–17.
[235] Y. Shi, L. Jia, H. Wen, Circ_0109046 promotes the progression of endometrial cancer via regulating miR-136/HMGA2 axis, Cancer Manag. Res. 12 (2020) 10993.
[236] J. Ma, F.-F. Kong, D. Yang, H. Yang, C. Wang, R. Cong, et al., lncRNA MIR210HG promotes the progression of endometrial cancer by sponging miR-337-3p/137 via the HMGA2-TGF-β/Wnt pathway, Mol. Ther. -Nucleic Acids 24 (2021) 905–922.
[237] Z. Shi, D. Wu, R. Tang, X. Li, R. Chen, S. Xue, et al., Silencing of HMGA2 promotes apoptosis and inhibits migration and invasion of prostate cancer cells, J. Biosci. 41 (2) (2016) 229–236.
[238] J. Cai, G. Shen, S. Liu, Q. Meng, Downregulation of HMGA2 inhibits cellular proliferation and invasion, improves cellular apoptosis in prostate cancer, Tumor Biol. 37 (1) (2016) 699–707.
[239] O. Hawsawi, V. Henderson, L.J. Burton, J. Dougan, P. Nagappan, V. Odero-Marah, High mobility group A2 (HMGA2) promotes EMT via MAPK pathway in prostate cancer, Biochem. Biophys. Res. Commun. 504 (1) (2018) 196–202.
[240] W. Huang, H. Zhang, Z. Jin, K. Li, C. Hu, M. Li, et al., MiR-219-5p inhibits prostate cancer cell growth and metastasis by targeting HMGA2, Eur. Rev. Med Pharm. Sci. 24 (9) (2020) 4710–4718.
[241] P. Wang, L. Zhang, S. Yin, Y. Xu, S. Tai, Zhang Li, et al., hsa_circ_0062019 promotes the proliferation, migration, and invasion of prostate cancer cells via the miR-195-5p/HMGA2 axis, Acta Biochim. Et. Biophys. Sin. 53 (7) (2021) 815–822.
[242] Z. Guo, C. He, F. Yang, L. Qin, X. Lu, J. Wu, Long non-coding RNA-NEAT1, a sponge for miR-98-5p, promotes expression of oncogene HMGA2 in prostate cancer, Biosci. Rep. 39 (2019) 9.
[243] H. Kaur, S.Z. Ali, L. Huey, M. Hütt-Cabezas, I. Taylor, X.-g Mao, et al., The transcriptional modulator HMGA2 promotes stemness and tumorigenicity in glioblastoma, Cancer Lett. 377 (1) (2016) 55–64.
[244] Y. Liu, S. Shete, C.J. Etzel, M. Scheurer, G. Alexiou, G. Armstrong, et al., Polymorphisms of LIG4, BTBD2, HMGA2, and RTEL1 genes involved in the double-strand break repair pathway predict glioblastoma survival, J. Clin. Oncol. 28 (14) (2010) 2467.
[245] J. Zhou, P. Wang, R. Zhang, X. Huang, H. Dai, L. Yuan, et al., Association of HMGA2 Polymorphisms with Glioma Susceptibility in Chinese Children, Pharm. Pers. Med. 14 (2021) 601.
[246] X. Zhong, X. Liu, Y. Li, M. Cheng, W. Wang, K. Tian, et al., HMGA2 sustains self-renewal and invasiveness of glioma-initiating cells, Oncotarget 7 (28) (2016) 44365.
[247] S. Zhang, H. Zhang, L. Yu, HMGA 2 promotes glioma invasion and poor prognosis via a long-range chromatin interaction, Cancer Med. 7 (7) (2018) 3226–3239.
[248] Nanotechnological based miRNA intervention in the therapeutic management of neuroblastoma, in: F.H. Pottoo, M.A. Barkat, M.A. Ansari, M.N. Javed, Q.M. S. Jamal, M.A. Kamal (Eds.), Seminars in Cancer Biology, Elsevier, 2021.
[249] J.M. Jiménez-Morales, Y.E. Hernández-Cuenca, A. Reyes-Abrahantes, H. Ruiz-García, F. Barajas-Olmos, H. García-Ortiz, et al., MicroRNA delivery systems in glioma therapy and perspectives: A systematic review, J. Control. Release 349 (2022) 712–730.
[250] V. Lulli, M. Buccarelli, R. Ilari, G. Castellani, C. De Dominicis, Di, A. Giamberardino, et al., Mir-370-3p impairs glioblastoma stem-like cell malignancy regulating a complex interplay between HMGA2/HIF1A and the oncogenic long non-coding RNA (lncRNA) NEAT1, Int. J. Mol. Sci. 21 (10) (2020) 3610.
[251] Gao Y-t, Chen X-b, H.-l Liu, Up-regulation of miR-370-3p restores glioblastoma multiforme sensitivity to temozolomide by influencing MGMT expression, Sci. Rep. 6 (1) (2016) 1–9.
[252] Z. Peng, T. Wu, Y. Li, Z. Xu, S. Zhang, B. Liu, et al., MicroRNA-370-3p inhibits human glioma cell proliferation and induces cell cycle arrest by directly targeting β-catenin, Brain Res. 1644 (2016) 53–61.
[253] A. Nadaradjane, J. Briand, G. Bougras-Cartron, V. Disdero, F.M. Vallette, J.-S. Frenel, et al., miR-370-3p is a therapeutic tool in anti-glioblastoma therapy but is not an intratumoral or cell-free circulating biomarker, Mol. Ther. -Nucleic Acids 13 (2018) 642–650.
[254] F. Zhang, A. Wu, Y. Wang, J. Liu, miR-490–3p functions as a tumor suppressor in glioma by inhibiting high-mobility group AT-hook 2 expression, Exp. Ther. Med. 18 (1) (2019) 664–670.
[255] D. Huang, S. Qiu, R. Ge, L. He, M. Li, Y. Li, et al., miR-340 suppresses glioblastoma multiforme, Oncotarget 6 (11) (2015) 9257.
[256] Y. Liu, X. Li, Y. Zhang, H. Wang, X. Rong, J. Peng, et al., An miR-340-5p-macrophage feedback loop modulates the progression and tumor microenvironment of glioblastoma multiforme, Oncogene 38 (49) (2019) 7399–7415.
[257] S. Asuthkar, K.K. Velpula, C. Chetty, B. Gorantla, J.S. Rao, Epigenetic regulation of miRNA-211 by MMP-9 governs glioma cell apoptosis, chemosensitivity and radiosensitivity, Oncotarget 3 (11) (2012) 1439.
[258] W. Li, X. Miao, L. Liu, Y. Zhang, X. Jin, X. Luo, et al., Methylation-mediated silencing of microRNA-211 promotes cell growth and epithelial to mesenchymal transition through activation of the AKT/β-catenin pathway in GBM, Oncotarget 8 (15) (2017) 25167.
[259] Y. Fan, M. Ye, L. Wu, S. Lv, M. Wu, B. Xiao, et al., Overexpression of miR-98 inhibits cell invasion in glioma cell lines via downregulation of IKKε, Age (years) 50 (31) (2015) 58.5.
[260] Y. Li, X. Wang, Z. Zhao, J. Shang, G. Li, R. Zhang, LncRNA NEAT1 promotes glioma cancer progression via regulation of miR-98-5p/BZW1, Biosci. Rep. 41 (2021) 7.
[261] X. Xu, Z. Bao, Y. Liu, J. Ji, N. Liu, MicroRNA-98 attenuates cell migration and invasion in glioma by directly targeting pre-B cell leukemia homeobox 3, Cell. Mol. Neurobiol. 37 (8) (2017) 1359–1371.
[262] B. Wang, X. Bu, H. Sun, Y. Liu, MicroRNA-98 promotes cell proliferation and invasion of glioblastoma via targeting HMGA2, J. Neurosurg. Sci. 64 (5) (2020) 496–497.
[263] L. Wang, Y. Tan, J. Chen, Z. Zhu, Y. Zhu, Q. Sun, et al., CircABCC1 promotes the development of glioma by sponging miR-591 and modulating high-mobility group A2, Ann. N. Y. Acad. Sci. 1511 (1) (2022) 107–118.
[264] W. Ni, Y. Xia, Y. Bi, F. Wen, D. Hu, L. Luo, FoxD2-AS1 promotes glioma progression by regulating miR-185–5 P/HMGA2 axis and PI3K/AKT signaling pathway, Aging (Albany NY) 11 (5) (2019) 1427.
[265] X. Liu, Y. Yidayitula, H. Zhao, Y. Luo, X. Ma, M. Xu, LncRNA LINC00152 promoted glioblastoma progression through targeting the miR-107 expression, Environ. Sci. Pollut. Res. 25 (18) (2018) 17674–17681.

[266] W. Wang, F. Wu, Z. Zhao, K.Y. Wang, R.Y. Huang, H.Y. Wang, et al., Long noncoding RNA LINC00152 is a potential prognostic biomarker in patients with high-grade glioma, CNS Neurosci. Ther. 24 (10) (2018) 957–966.
[267] J. Cai, J. Zhang, P. Wu, W. Yang, Q. Ye, Q. Chen, et al., Blocking LINC00152 suppresses glioblastoma malignancy by impairing mesenchymal phenotype through the miR-612/AKT2/NF-κB pathway, J. Neuro-Oncol. 140 (2) (2018) 225–236.
[268] J. Sakata, A. Hirosue, R. Yoshida, K. Kawahara, Y. Matsuoka, T. Yamamoto, et al., HMGA2 contributes to distant metastasis and poor prognosis by promoting angiogenesis in oral squamous cell carcinoma, Int. J. Mol. Sci. 20 (10) (2019) 2473.
[269] H. Yamazaki, T. Mori, M. Yazawa, A.M. Maeshima, F. Matsumoto, S. Yoshimoto, et al., Stem cell self-renewal factors Bmi1 and HMGA2 in head and neck squamous cell carcinoma: clues for diagnosis, Lab. Investig. 93 (12) (2013) 1331–1338.
[270] K.-P. Chang, S.-J. Lin, S.-C. Liu, J.-S. Yi, K.-Y. Chien, L.-M. Chi, et al., Low-molecular-mass secretome profiling identifies HMGA2 and MIF as prognostic biomarkers for oral cavity squamous cell carcinoma, Sci. Rep. 5 (1) (2015) 1–17.
[271] Z. Li, X. Wu, J. Li, S. Yu, X. Ke, T. Yan, et al., HMGA2-Snai2 axis regulates tumorigenicity and stemness of head and neck squamous cell carcinoma, Exp. Cell Res. 418 (1) (2022), 113271.
[272] Jr.A. Palumbo, N.M. Da Costa, F. Esposito, M. De Martino, D. D'Angelo, V.P.L. de Sousa, et al., HMGA2 overexpression plays a critical role in the progression of esophageal squamous carcinoma, Oncotarget 7 (18) (2016) 25872.
[273] C.-Y. Fang, P.-L. Liew, C.-L. Chen, Y.-H. Lin, C.-L. Fang, W.-Y. Chen, High HMGA2 expression correlates with reduced recurrence-free survival and poor overall survival in oral squamous cell carcinoma, Anticancer Res. 37 (4) (2017) 1891–1899.
[274] L. Xu, W.-L. Liao, Q.-J. Lu, C.-G. Li, Y. Yuan, Z.-Y. Xu, et al., ANG promotes proliferation and invasion of the cell of lung squamous carcinoma by directly up-regulating HMGA2, J. Cancer 7 (7) (2016) 862.
[275] W. Ha, A. Hinde, L. Xie, M.H. Trager, L. Liu, Biomarker function of HMGA2 in ultraviolet-induced skin cancer development, Exp. Dermatol. 29 (10) (2020) 1021–1026.
[276] M. Zhu, C. Zhang, D. Chen, S. Chen, H. Zheng, MicroRNA-98-HMGA2-POSTN signal pathway reverses epithelial-to-mesenchymal transition in laryngeal squamous cell carcinoma, Biomed. Pharmacother. 117 (2019), 108998.
[277] L.-J. Ma, J. Wu, E. Zhou, J. Yin, X.-P. Xiao, Molecular mechanism of targeted inhibition of HMGA2 via miRNAlet-7a in proliferation and metastasis of laryngeal squamous cell carcinoma, Biosci. Rep. 40 (2020) 6.
[278] B. Hou, H. Ishinaga, K. Midorikawa, S. Nakamura, Y. Hiraku, S. Oikawa, et al., Let-7c inhibits migration and epithelial–mesenchymal transition in head and neck squamous cell carcinoma by targeting IGF1R and HMGA2, Oncotarget 9 (10) (2018) 8927.
[279] Xue F., Feng H., Wang T., Feng G., Ni N., Wang R., et al. hsa_circ_0000264 promotes tumor progression via the hsa-let-7b-5p/HMGA2 axis in head and neck squamous cell carcinoma. Oral Diseases, 2022.
[280] A. Agostini, I. Panagopoulos, H.K. Andersen, L.E. Johannesen, B. Davidson, C. G. Tropé, et al., HMGA2 expression pattern and TERT mutations in tumors of the vulva, Oncol. Rep. 33 (6) (2015) 2675–2680.
[281] A. Fatalska, N. Rusetska, E. Bakuła-Zalewska, A. Kowalik, S. Zięba, A. Wroblewska, et al., Inflammatory proteins HMGA2 and PRTN3 as drivers of vulvar squamous cell carcinoma progression, Cancers 13 (1) (2020) 27.
[282] A. Agostini, M. Brunetti, B. Davidson, C.G. Trope, S. Heim, I. Panagopoulos, et al., Expressions of miR-30c and let-7a are inversely correlated with HMGA2 expression in squamous cell carcinoma of the vulva, Oncotarget 7 (51) (2016) 85058.
[283] L. Dong, F. Qu, CircUBAP2 promotes SEMA6D expression to enhance the cisplatin resistance in osteosarcoma through sponging miR-506-3p by activating Wnt/β-catenin signaling pathway, J. Mol. Histol. 51 (4) (2020) 329–340.
[284] H. Wu, W. Li, S. Zhu, D. Zhang, M. Zhang, Circular RNA circUBAP2 regulates proliferation and invasion of osteosarcoma cells through miR-641/YAP1 axis, Cancer Cell Int. 20 (1) (2020) 1–12.
[285] H. Zhang, G. Wang, C. Ding, P. Liu, R. Wang, W. Ding, et al., Increased circular RNA UBAP2 acts as a sponge of miR-143 to promote osteosarcoma progression, Oncotarget 8 (37) (2017) 61687.
[286] W. Ma, N. Xue, J. Zhang, D. Wang, X. Yao, L. Lin, et al., circUBAP2 regulates osteosarcoma progression via the miR-204–3p/HMGA2 axis, Int. J. Oncol. 58 (3) (2021) 298–311.
[287] W. Ma, X. Zhao, Y. Gao, X. Yao, J. Zhang, Q. Xu, Circular RNA circ_UBAP2 facilitates the progression of osteosarcoma by regulating microRNA miR-637/high-mobility group box (HMGB) 2 axis, Bioengineered 13 (2) (2022) 4411–4427.
[288] M. Li, Y. Shen, Q. Wang, X. Zhou, MiR-204-5p promotes apoptosis and inhibits migration of osteosarcoma via targeting EBF2, Biochimie 158 (2019) 224–232.
[289] J. He, J. Guan, S. Liao, Z. Wu, B. Liu, H. Mo, et al., Long noncoding RNA CCDC144NL-AS1 promotes the oncogenicity of osteosarcoma by acting as a molecular sponge for microRNA-490-3p and thereby increasing HMGA2 expression, OncoTargets Ther. 14 (2021) 1.
[290] W. Ma, Y. Gao, J. Zhang, X. Yao, L. Jia, Q. Xu, Long noncoding RNA LINC01410 promotes tumorigenesis of osteosarcoma cells via miR-497–5p/HMGA2 axis, J. Biochem. Mol. Toxicol. 35 (12) (2021), e22921.
[291] L. Ge, B. Zheng, M. Li, L. Niu, Z. Li, MicroRNA-497 suppresses osteosarcoma tumor growth in vitro and in vivo, Oncol. Lett. 11 (3) (2016) 2207–2212.
[292] Z. Gui, T. Wu, G. Zhao, Z. Lin, H. Xu, MicroRNA-497 suppress osteosarcoma by targeting MAPK/Erk pathway, Bratisl. Lek. Listy 118 (8) (2017) 449–452.
[293] X.-j Shao, M.-h Miao, J. Xue, J. Xue, X.-q Ji, H. Zhu, The down-regulation of microRNA-497 contributes to cell growth and cisplatin resistance through PI3K/Akt pathway in osteosarcoma, Cell. Physiol. Biochem. 36 (5) (2015) 2051–2062.
[294] Q. Xu, L. He, L. Ma, L. Fan, L. Yan, X. Zhao, et al., LINC01410 accelerated the invasion and proliferation of osteosarcoma by sponging miR-3128, Aging (Albany NY) 12 (24) (2020) 24957.
[295] W. Ma, X. Zhao, N. Xue, Y. Gao, Q. Xu, The LINC01410/miR-122–5p/NDRG3 axis is involved in the proliferation and migration of osteosarcoma cells, Iubmb Life 73 (4) (2021) 705–717.
[296] F. Song, Y. Yang, J. Liu, Expression and significances of MiRNA Let-7 and HMGA2 in laryngeal carcinoma, Eur. Rev. Med Pharm. Sci. 20 (21) (2016) 4452–4458.
[297] Jr.A. Palumbo, M. De Martino, F. Esposito, F. Fraggetta, P.N. Neto, P. Valverde Fernandes, et al., HMGA 2, but not HMGA 1, is overexpressed in human larynx carcinomas, Histopathology 72 (7) (2018) 1102–1114.
[298] L. Raskin, D.R. Fullen, T.J. Giordano, D.G. Thomas, M.L. Frohm, K.B. Cha, et al., Transcriptome profiling identifies HMGA2 as a biomarker of melanoma progression and prognosis, J. Invest. Dermatol. 133 (11) (2013) 2585–2592.
[299] X. Hou, W. Wan, J. Wang, M. Li, Y. Wang, Y. Yao, et al., Let-7a inhibits migration of melanoma cells via down-regulation of HMGA2 expression, Am. J. Transl. Res. 8 (9) (2016) 3656.
[300] N. Venkatesan, M. Kandalam, G. Pasricha, V. Sumantran, G. Manfioletti, S.J. Ono, et al., Expression of high mobility group A2 protein in retinoblastoma and its association with clinicopathologic features, J. Pediatr. Hematol. /Oncol. 31 (3) (2009) 209–214.
[301] W. Li, J. Wang, D. Zhang, X. Zhang, J. Xu, L. Zhao, MicroRNA-98 targets HMGA2 to inhibit the development of retinoblastoma through mediating Wnt/β-catenin pathway, Cancer Biomark. 25 (1) (2019) 79–88.
[302] Y.-Y. Xia, L. Yin, H. Tian, W.-J. Guo, N. Jiang, X.-S. Jiang, et al., HMGA2 is associated with epithelial–mesenchymal transition and can predict poor prognosis in nasopharyngeal carcinoma, OncoTargets Ther. 8 (2015) 169.
[303] Y.-y Xia, L. Yin, N. Jiang, W.-J. Guo, H. Tian, X.-S. Jiang, et al., Downregulating HMGA2 attenuates epithelial-mesenchymal transition-induced invasion and migration in nasopharyngeal cancer cells, Biochem. Biophys. Res. Commun. 463 (3) (2015) 357–363.
[304] A. Wu, K. Wu, J. Li, Y. Mo, Y. Lin, Y. Wang, et al., Let-7a inhibits migration, invasion and epithelial-mesenchymal transition by targeting HMGA2 in nasopharyngeal carcinoma, J. Transl. Med. 13 (1) (2015) 1–13.
[305] R. Ma, P. Gao, H. Yang, J. Hu, J.-J. Xiao, M. Shi, et al., Inhibition of cell proliferation and radioresistance by miR-383-5p through targeting RNA binding protein motif (RBM3) in nasopharyngeal carcinoma, Ann. Transl. Med. 9 (2021) 2.
[306] C. Gao, W. Lu, W. Lou, L. Wang, Q. Xu, Long noncoding RNA HOXC13–AS positively affects cell proliferation and invasion in nasopharyngeal carcinoma via modulating miR-383–3p/HMGA2 axis, J. Cell. Physiol. 234 (8) (2019) 12809–12820.
[307] H. Zhou, W. Guo, Y. Zhao, Y. Wang, R. Zha, J. Ding, et al., MicroRNA-26a acts as a tumor suppressor inhibiting gallbladder cancer cell proliferation by directly targeting HMGA2, Int. J. Oncol. 44 (6) (2014) 2050–2058.
[308] H. Zhao, H. Zhao, X. Xia, X. Liu, MicroRNA-599 targets high-mobility group AT-hook 2 to inhibit cell proliferation and invasion in clear cell renal carcinoma, Mol. Med. Rep. 17 (5) (2018) 7451–7459.
[309] Zh Ye, Dw Gui, Xy Wang, J. Wang, Jl Fu, LncRNA SNHG1 promotes renal cell carcinoma progression through regulation of HMGA2 via sponging miR-103a, J. Clin. Lab. Anal. (2022), e24422.
[310] P. Ramos, M. Bentires-Alj, Mechanism-based cancer therapy: resistance to therapy, therapy for resistance, Oncogene 34 (28) (2015) 3617–3626.
[311] Y. Sun, Tumor microenvironment and cancer therapy resistance, Cancer Lett. 380 (1) (2016) 205–215.
[312] N. Vasan, J. Baselga, D.M. Hyman, A view on drug resistance in cancer, Nature 575 (7782) (2019) 299–309.
[313] G. Housman, S. Byler, S. Heerboth, K. Lapinska, M. Longacre, N. Snyder, et al., Drug resistance in cancer: an overview, Cancers 6 (3) (2014) 1769–1792.
[314] X. Wang, H. Zhang, X. Chen, Drug resistance and combating drug resistance in cancer, Cancer Drug Resist. 2 (2) (2019) 141.
[315] C. Holohan, S. Van Schaeybroeck, D.B. Longley, P.G. Johnston, Cancer drug resistance: an evolving paradigm, Nat. Rev. Cancer 13 (10) (2013) 714–726.
[316] E. Galle, B. Thienpont, S. Cappuyns, T. Venken, P. Busschaert, M. Van Haele, et al., DNA methylation-driven EMT is a common mechanism of resistance to various therapeutic agents in cancer, Clin. Epigenet. 12 (2020) 1–19.
[317] J. Halder, D. Pradhan, B. Kar, G. Ghosh, G. Rath, Nanotherapeutics approaches to overcome P-glycoprotein-mediated multi-drug resistance in cancer, Nanomed.: Nanotechnol., Biol. Med. 40 (2022), 102494.
[318] M. Karami Fath, A. Azargoonjahromi, A. Kiani, F. Jalalifar, P. Osati, M. Akbari Oryani, et al., The role of epigenetic modifications in drug resistance and treatment of breast cancer, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–25.
[319] C. Zhang, X. Liu, S. Jin, Y. Chen, R. Guo, Ferroptosis in cancer therapy: a novel approach to reversing drug resistance, Mol. Cancer 21 (1) (2022) 47.
[320] M. Vaghari-Tabari, P. Hassanpour, F. Sadeghsoltani, F. Malakoti, F. Alemi, D. Qujeq, et al., CRISPR/Cas9 gene editing: A new approach for overcoming drug resistance in cancer, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–29.
[321] S. Pan, D. Bao, Y. Li, D. Liu, S. Quan, R. Wang, SOX4 induces drug resistance of colorectal cancer cells by downregulating CYLD through transcriptional activation of microRNA-17, J. Biochem. Mol. Toxicol. 36 (1) (2022), e22910.
[322] T. Zhu, Z. Hu, Z. Wang, H. Ding, R. Li, J. Wang, et al., microRNA-301b-3p from mesenchymal stem cells-derived extracellular vesicles inhibits TXNIP to promote multidrug resistance of gastric cancer cells, Cell Biol. Toxicol. (2022) 1–15.

[323] M. Tamai, S. Tatarano, S. Okamura, W. Fukumoto, I. Kawakami, Y. Osako, et al., microRNA-99a-5p induces cellular senescence in gemcitabine-resistant bladder cancer by targeting SMARCD1, Mol. Oncol. 16 (6) (2022) 1329.
[324] T.-H. Jang, W.-C. Huang, S.-L. Tung, S.-C. Lin, P.-M. Chen, C.-Y. Cho, et al., MicroRNA-485-5p targets keratin 17 to regulate oral cancer stemness and chemoresistance via the integrin/FAK/Src/ERK/β-catenin pathway, J. Biomed. Sci. 29 (1) (2022) 1–20.
[325] M. Li, Z. Li, J. Song, X. Li, P. Zhai, X. Mu, et al., miR-205 Reverses MDR-1 Mediated Doxorubicin Resistance via PTEN in Human Liver Cancer HepG2 Cells, Cell J. (Yakhteh) 24 (3) (2022) 112.
[326] J.C.-W. Ho, J. Chen, I.W.-Y. Cheuk, M.-T. Siu, V.Y. Shin, A. Kwong, MicroRNA-199a-3p promotes drug sensitivity in triple negative breast cancer by down-regulation of BRCA1, Am. J. Transl. Res. 14 (3) (2022) 2021.
[327] X. Lu, R. Liu, M. Wang, A.K. Kumar, F. Pan, L. He, et al., MicroRNA-140 impedes DNA repair by targeting FEN1 and enhances chemotherapeutic response in breast cancer, Oncogene 39 (1) (2020) 234–247.
[328] H. Li, Y. Lei, S. Li, F. Li, J. Lei, MicroRNA-20a-5p inhibits the autophagy and cisplatin resistance in ovarian cancer via regulating DNMT3B-mediated DNA methylation of RBP1, Reprod. Toxicol. 109 (2022) 93–100.
[329] L. Qiu, J. Wang, M. Chen, F. Chen, W. Tu, Exosomal microRNA-146a derived from mesenchymal stem cells increases the sensitivity of ovarian cancer cells to docetaxel and taxane via a LAMC2–mediated PI3K/Akt axis, Int. J. Mol. Med. 46 (2) (2020) 609–620.
[330] M. Liu, C. Gong, R. Xu, Y. Chen, X. Wang, MicroRNA-5195-3p enhances the chemosensitivity of triple-negative breast cancer to paclitaxel by downregulating EIF4A2, Cell. Mol. Biol. Lett. 24 (2019) 1–11.
[331] P. Zhao, Y.-g Ma, Y. Zhao, D. Liu, Z.-j Dai, C.-y Yan, et al., MicroRNA-552 deficiency mediates 5-fluorouracil resistance by targeting SMAD2 signaling in DNA-mismatch-repair-deficient colorectal cancer, Cancer Chemother. Pharmacol. 84 (2019) 427–439.
[332] Y. Gao, W. Zhang, C. Liu, G. Li, miR-200 affects tamoxifen resistance in breast cancer cells through regulation of MYB, Sci. Rep. 9 (1) (2019) 18844.
[333] H. Wang, S. Ren, Y. Xu, W. Miao, X. Huang, Z. Qu, et al., MicroRNA-195 reverses the resistance to temozolomide through targeting cyclin E1 in glioma cells, Anti-Cancer Drugs 30 (1) (2019) 81.
[334] Y. Wu, Y. Yao, Y. Yun, M. Wang, R. Zhu, MicroRNA-302c enhances the chemosensitivity of human glioma cells to temozolomide by suppressing P-gp expression, Biosci. Rep. 39 (2019) 9.
[335] X. Jing, M. Xie, K. Ding, T. Xu, Y. Fang, P. Ma, et al., Exosome-transmitted miR-769–5p confers cisplatin resistance and progression in gastric cancer by targeting CASP9 and promoting the ubiquitination degradation of p53, Clin. Transl. Med. 12 (5) (2022) e780.
[336] S. Zhao, T. Pan, J. Deng, L. Cao, J.M. Vicencio, J. Liu, et al., Exosomal transfer of miR-181b-5p confers senescence-mediated doxorubicin resistance via modulating BCLAF1 in breast cancer, Br. J. Cancer (2022) 1–13.
[337] S. Gasiulė, N. Dreize, A. Kaupinis, R. Ražanskas, L. Čiupas, V. Stankevičius, et al., Molecular insights into miRNA-driven resistance to 5-fluorouracil and oxaliplatin chemotherapy: miR-23b modulates the epithelial–mesenchymal transition of colorectal cancer cells, J. Clin. Med. 8 (12) (2019) 2115.
[338] B. Liu, J. Hu, H. Zhao, L. Zhao, S. Pan, MicroRNA-155-5p contributes to 5-fluorouracil resistance through down-regulating TP53INP1 in oral squamous cell carcinoma, Front. Oncol. 11 (2022) 5666.
[339] C. Wu, A. Zhao, T. Tan, Y. Wang, Z. Shen, Overexpression of microRNA-620 facilitates the resistance of triple negative breast cancer cells to gemcitabine treatment by targeting DCTD, Exp. Ther. Med. 18 (1) (2019) 550–558.
[340] S. Li, W. Li, G. Chen, J. Huang, W. Li, MiRNA-27a-3p induces temozolomide resistance in glioma by inhibiting NF1 level, Am. J. Transl. Res. 12 (8) (2020) 4749.
[341] Z. Han, C. Zhang, Q. Wang, L. Li, M. Wang, X. Li, et al., MicroRNA-19b downregulates NR3C1 and enhances oxaliplatin chemoresistance in colon cancer via the PI3K/AKT/mTOR pathway, Clin. Med. Insight.: Oncol. 15 (2021), 11795549211012666.
[342] S.E. Park, W. Kim, J.-Y. Hong, D. Kang, S. Park, J. Suh, et al., miR-96-5p targets PTEN to mediate sunitinib resistance in clear cell renal cell carcinoma, Sci. Rep. 12 (1) (2022) 3537.
[343] C. Holjencin, A. Jakymiw, MicroRNAs and Their Big Therapeutic Impacts: Delivery Strategies for Cancer Intervention, Cells 11 (15) (2022) 2332.
[344] M. Zare, R. Pemmada, M. Madhavan, A. Shailaja, S. Ramakrishna, S.P. Kandiyil, et al., Encapsulation of miRNA and siRNA into Nanomaterials for Cancer Therapeutics, Pharmaceutics 14 (8) (2022) 1620.
[345] E. Oveili, S. Vafaei, H. Bazavar, Y. Eslami, E. Mamaghanizadeh, S. Yasamineh, et al., The potential use of mesenchymal stem cells-derived exosomes as microRNAs delivery systems in different diseases, Cell Commun. Signal. 21 (1) (2023) 1–26.
[346] G. Kara, B. Arun, G.A. Calin, B. Ozpolat, miRacle of microRNA-Driven Cancer Nanotherapeutics, Cancers 14 (15) (2022) 3818.
[347] Q. Tang, D. Liu, H. Chen, D. He, W. Pan, Q. Li, et al., Functionalized PAMAM-Based system for targeted delivery of miR-205 and 5-fluorouracil in breast cancer, J. Drug Deliv. Sci. Technol. 67 (2022), 102959.
[348] F.N. Golafzani, A.Z. Vaziri, M. Javanmardi, F. Seyfan, M. Yazdanifar, S. Khaleghi, Delivery of miRNA-126 through folic acid-targeted biocompatible polymeric nanoparticles for effective lung cancer therapy, J. Bioact. Compat. Polym. 37 (3) (2022) 168–188.
[349] D. Li, L. Gong, H. Lin, S. Yao, Y. Yin, Z. Zhou, et al., Hyaluronic Acid-Coated Bovine Milk Exosomes for Achieving Tumor-Specific Intracellular Delivery of miRNA-204, Cells 11 (19) (2022) 3065.
[350] H. Nie, X. Xie, D. Zhang, Y. Zhou, B. Li, F. Li, et al., Use of lung-specific exosomes for miRNA-126 delivery in non-small cell lung cancer, Nanoscale 12 (2) (2020) 877–887.
[351] X. Xin, F. Lin, Q. Wang, L. Yin, R.I. Mahato, ROS-responsive polymeric micelles for triggered simultaneous delivery of PLK1 inhibitor/miR-34a and effective synergistic therapy in pancreatic cancer, ACS Appl. Mater. Interfaces 11 (16) (2019) 14647–14659.
[352] Y. Wu, Y. Tang, S. Xie, X. Zheng, S. Zhang, J. Mao, et al., Chimeric peptide supramolecular nanoparticles for plectin-1 targeted miRNA-9 delivery in pancreatic cancer, Theranostics 10 (3) (2020) 1151.
[353] R. Conte, A. Valentino, F. Di Cristo, G. Peluso, P. Cerruti, A. Di Salle, et al., Cationic polymer nanoparticles-mediated delivery of miR-124 impairs tumorigenicity of prostate cancer cells, Int. J. Mol. Sci. 21 (3) (2020) 869.
[354] C.H. Kapadia, S.A. Ioele, E.S. Day, Layer-by-layer assembled PLGA nanoparticles carrying miR-34a cargo inhibit the proliferation and cell cycle progression of triple-negative breast cancer cells, J. Biomed. Mater. Res. Part A 108 (3) (2020) 601–613.
[355] J. Peng, R. Wang, W. Sun, M. Huang, R. Wang, Y. Li, et al., Delivery of miR-320a-3p by gold nanoparticles combined with photothermal therapy for directly targeting Sp1 in lung cancer, Biomater. Sci. 9 (19) (2021) 6528–6541.
[356] M. Moro, D. Di Paolo, M. Milione, G. Centonze, V. Bornaghi, C. Borzi, et al., Coated cationic lipid-nanoparticles entrapping miR-660 inhibit tumor growth in patient-derived xenografts lung cancer models, J. Control. Release 308 (2019) 44–56.
[357] L. Jiang, Y. Zhang, L. Guo, C. Liu, P. Wang, W. Ren, Exosomal microRNA-107 reverses chemotherapeutic drug resistance of gastric cancer cells through HMGA2/mTOR/P-gp pathway, BMC Cancer 21 (1) (2021) 1–16.
[358] X. Yang, Q. Zhao, H. Yin, X. Lei, R. Gan, MiR-33b-5p sensitizes gastric cancer cells to chemotherapy drugs via inhibiting HMGA2 expression, J. Drug Target. 25 (7) (2017) 653–660.
[359] L. Liang, H. Kang, J. Jia, HCP5 contributes to cisplatin resistance in gastric cancer through miR-128/HMGA2 axis, Cell Cycle 20 (11) (2021) 1080–1090.
[360] H. Wu, Y. Liang, L. Shen, L. Shen, MicroRNA-204 modulates colorectal cancer cell sensitivity in response to 5-fluorouracil-based treatment by targeting high mobility group protein A2, Biol. Open 5 (5) (2016) 563–570.
[361] H. Zheng, B. Yan, Q. Wu, J. Zhang, MicroRNA-9–5p increases the sensitivity of colorectal cancer cells to 5–fluorouracil by downregulating high mobility group A2 expression, Oncol. Lett. 21 (3) (2021) 1.
[362] H. Wu, Q. Zou, H. He, Y. Liang, M. Lei, Q. Zhou, et al., Long non-coding RNA PCAT6 targets miR-204 to modulate the chemoresistance of colorectal cancer cells to 5–fluorouracil-based treatment through HMGA2 signaling, Cancer Med. 8 (5) (2019) 2484–2495.
[363] M. Zhu, Y. Wang, F. Wang, L. Li, X. Qiu, CircFBXL5 promotes the 5-FU resistance of breast cancer via modulating miR-216b/HMGA2 axis, Cancer Cell Int. 21 (1) (2021) 1–12.
[364] S. Yang, C. Zou, Y. Li, X. Yang, W. Liu, G. Zhang, et al., Knockdown circTRIM28 enhances tamoxifen sensitivity via the miR-409-3p/HMGA2 axis in breast cancer, Reprod. Biol. Endocrinol. 20 (1) (2022) 1–13.
[365] Y. Yang, P. Zhang, Y. Zhao, J. Yang, G. Jiang, J. Fan, Decreased MicroRNA-26a expression causes cisplatin resistance in human non-small cell lung cancer, Cancer Biol. Ther. 17 (5) (2016) 515–525.
[366] Z. Song, C. Liao, L. Yao, X. Xu, X. Shen, S. Tian, et al., miR-219-5p attenuates cisplatin resistance of ovarian cancer by inactivating Wnt/β-catenin signaling and autophagy via targeting HMGA2, Cancer Gene Ther. (2022) 1–12.
[367] J.-T. Miao, J.-H. Gao, Y.-Q. Chen, H. Chen, H.-Y. Meng, G. Lou, LncRNA ANRIL affects the sensitivity of ovarian cancer to cisplatin via regulation of let-7a/HMGA2 axis, Biosci. Rep. 39 (2019) 7.
[368] S. Ma, T. Fu, S. Zhao, M. Gao, MicroRNA-34a-5p suppresses tumorigenesis and progression of glioma and potentiates Temozolomide-induced cytotoxicity for glioma cells by targeting HMGA2, Eur. J. Pharmacol. 852 (2019) 42–50.
[369] W.Q. Jia, J.W. Zhu, C.Y. Yang, J. Ma, T.Y. Pu, G.Q. Han, et al., Verbascoside inhibits progression of glioblastoma cells by promoting Let-7g-5p and down-regulating HMGA2 via Wnt/beta-catenin signalling blockade, J. Cell. Mol. Med. 24 (5) (2020) 2901–2916.