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Review

The emerging role of non-coding RNAs in the regulation of PI3K/AKT pathway in the carcinogenesis process

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ABSTRACT

The PI3K/AKT pathway is an intracellular signaling pathway with an indispensable impact on cell cycle control. This pathway is functionally related with cell proliferation, cell survival, metabolism, and quiescence. The crucial role of this pathway in the development of cancer has offered this pathway as a target of novel anti-cancer treatments. Recent researches have demonstrated the role of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in controlling the PI3K/AKT pathway. Some miRNAs such as miR-155-5p, miR-328-3p, miR-125b-5p, miR-126, miR-331-3p and miR-16 inactivate this pathway, while miR-182, miR-106a, miR-193, miR-214, miR-106b, miR-93, miR-21 and miR-103/107 enhance activity of this pathway. Expression levels of PI3K/AKT-associated miRNAs could be used to envisage the survival of cancer patients. Numerous lncRNAs such as GAS5, FER1L4, LINC00628, PICART1, LOC101928316, ADAMTS9-AS2, SLC25A5-AS1, MEG3, AB073614 and SNHG6 interplay with this pathway. Identification of the impact of miRNAs and lncRNAs in the control of the activity of PI3K/AKT pathway would enhance the efficacy of targeted therapies against this pathway. Moreover, each of the mentioned miRNAs and lncRNAs could be used as a putative therapeutic candidate for the interfering with the carcinogenesis. In the current study, we review the role of miRNAs and lncRNAs in controlling the PI3K/AKT pathway and their contribution to carcinogenesis.

1. Introduction

The PI3K/AKT pathway is an intracellular signaling cascade with an indispensable effect on cell cycle. This pathway is functionally associated with cell proliferation, quiescence, and cancer [1]. PI3K can be triggered by receptor tyrosine kinases, G protein-coupled receptors, and small-GTPases. Subsequently, PI3K can facilitate the conversion of PIP2 to PIP3 which leads to the recruitment of PH-domain-containing membrane proteins including AKT and mTORC2 [2]. When PI3K is activated, it initiates a number of reactions that finally phosphorylates and activates AKT [1]. Activation of AKT leads to several effects including CREB activation [3], suppression of p27 activity [4], modulation of FOXO subcellular localization, and activation of mTOR [4]. Several factors such as EGF [5], shh [3], IGF-1 [3], insulin [4], and CaM [6] have been identified as activators of the PI3K/AKT pathway. On the other hand, PTEN [7], GSK3B [3], HB9 [5], and SHIP1/2 and INPP4B [2] are known as inhibitors of this pathway. The role of PI3K in carcinogenesis has been initially discovered more than three decades ago through the observed association between this protein and the transforming function of viral oncogenes [8]. Several years later, independent studies revealed mutations in PIK3R1 [9] and PIK3CA [10] genes in numerous kinds of solid tumors, further highlighting the association between PI3K and carcinogenesis. Subsequently, PIK3CA was recognized as one of the most commonly activated oncogenes in diverse malignancies [11,12]. Moreover, up-regulation of the activity of the PI3K/AKT pathway has been demonstrated in many cancers, leading to impediment of apoptosis and augmentation of cell proliferation [2]. Such a process is exerted via modulation of numerous main nodes of the pathway [13]. Fig. 1depicts

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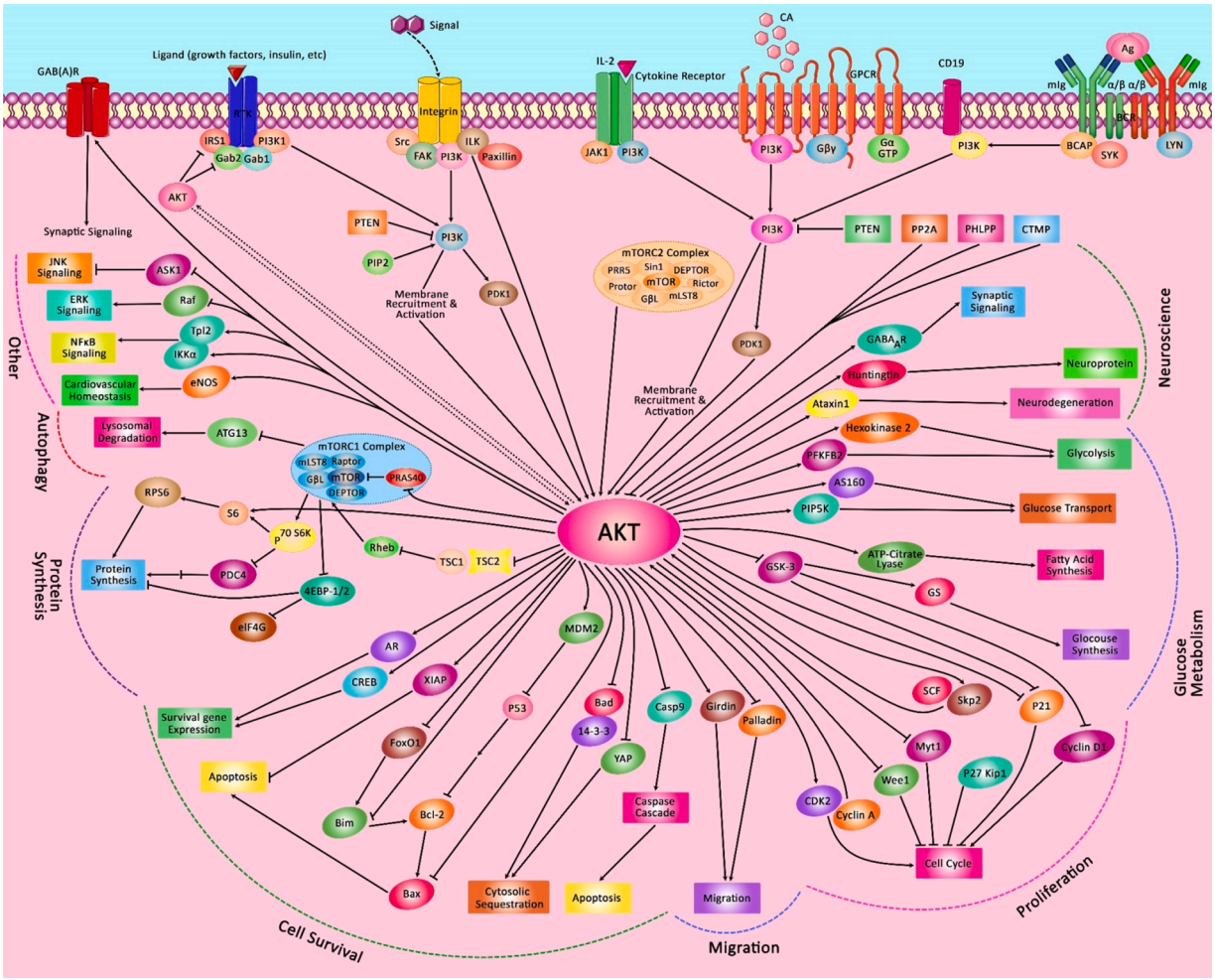

Fig. 1. A schematic diagram of the PI3K/AKT/mTOR pathway. AKT, or alternatively named as protein kinase B (PKB) is a serine/threonine kinase with an effective regulatory role in various cellular survival pathways, principally as a suppressor of apoptosis as well as cellular processes of oncogenesis, angiogenesis, autophagy and metabolism. Dysregulation of the PI3K/AKT pathway is involved in various human diseases namely neoplasms, diabetes, cardiovascular disorders, and neurological disorders. Binding of a growth factor (e.g., EGF, HGF, PDGF, and VEGF) to RTK could activate this receptor tyrosine kinase. PI3K is composed of two subunits namely p85 and p110. PI3K could bind to IRS-1, RTK, or GPCR and trigger the enzymatic function of the p110 subunit, which then synthesizes PIP3 in the membrane. The accessibility of PIP3 at the plasma membrane could be controlled by the contrary functions of PI3K, that phosphorylates PIP2 to PIP3, and PTEN, that dephosphorylates PIP3 and inhibits recruitment of AKT. Subsequently, AKT is recruited to the membrane. Activation of AKT1 could partake in the downstream regulation of protein complexes mTORC1 and mTORC2 that could in turn trigger gene transcription and elevate cell growth and cell survival. The activated AKT kinase could phosphorylate different substrates including PRAS40 that is subsequently inactivated and releases mTORC1. Furthermore, TSC2 is suppressed, while the downstream GTPase Rheb remains GTP-bound and thereby could regulate mTORC1. Activation of mTORC1 complex could alternatively regulates translation machinery proteins via 4E-BP1 or S6K-1 phosphorylation. AKT signaling have a remarkable role in various human cancers which can pave the way for anti-cancer therapeutics. Numerous non-coding RNAs (ncRNAs) have been confirmed to alter the activity of the PI3K/AKT cascade. We review the effect of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) on PI3K/AKT pathway and their contribution to carcinogenesis.

an overview of PI3K/AKT signaling cascade which plays a significant role in the regulation of various cellular survival pathways like JNK, ERK, NFκB, and is involved in the cardiovascular homeostasis, glucose metabolism as well as synaptic signaling.

2. FmiRNAs and PI3K/AKT pathway

Numerous miRNAs are connected with PI3K/AKT pathway and the pathogenesis of human cancers. Both up-regulated and down-regulated miRNAs in cancers are implicated in this process.

3. Down-regulated PI3K/AKT-associated miRNAs in cancers

Expression of miR-155-5p has been down-regulated in both blood and tumor sections of patients with Wilms' tumor (WT) who did not get chemotherapy prior to surgery but was increased in tumor samples of those who had received chemotherapy prior to surgery. Moreover, expression levels of IGF2, PI3K, AKT, and mTOR have been increased in WT tissues. Further studies indicated that this miRNA acts as a tumor suppressor in this type of malignancy via inhibiting the PI3K/AKT/mTOR cascade. This function is mediated through the inhibition of IGF2 by miR-155-5p [14]. miR-328-3p has been down-regulated in bladder cancer tissues in association with the poor prognosis of patients. Mechanistically, this miRNA blocks cell proliferation, migratory aptitude, and invasiveness via binding with 3' untranslated region (UTR) of ITGA5, thus suppressing epithelial-mesenchymal transition (EMT) and inactivating PI3K/AKT signaling in bladder cancer tissues [15]. Other investigations in bladder cancer samples revealed down-regulation of miR-125b-5p in cancer tissues and cell lines. Notably, down-regulation of miR-125b-5p has been linked with poor patients' survival, a higher

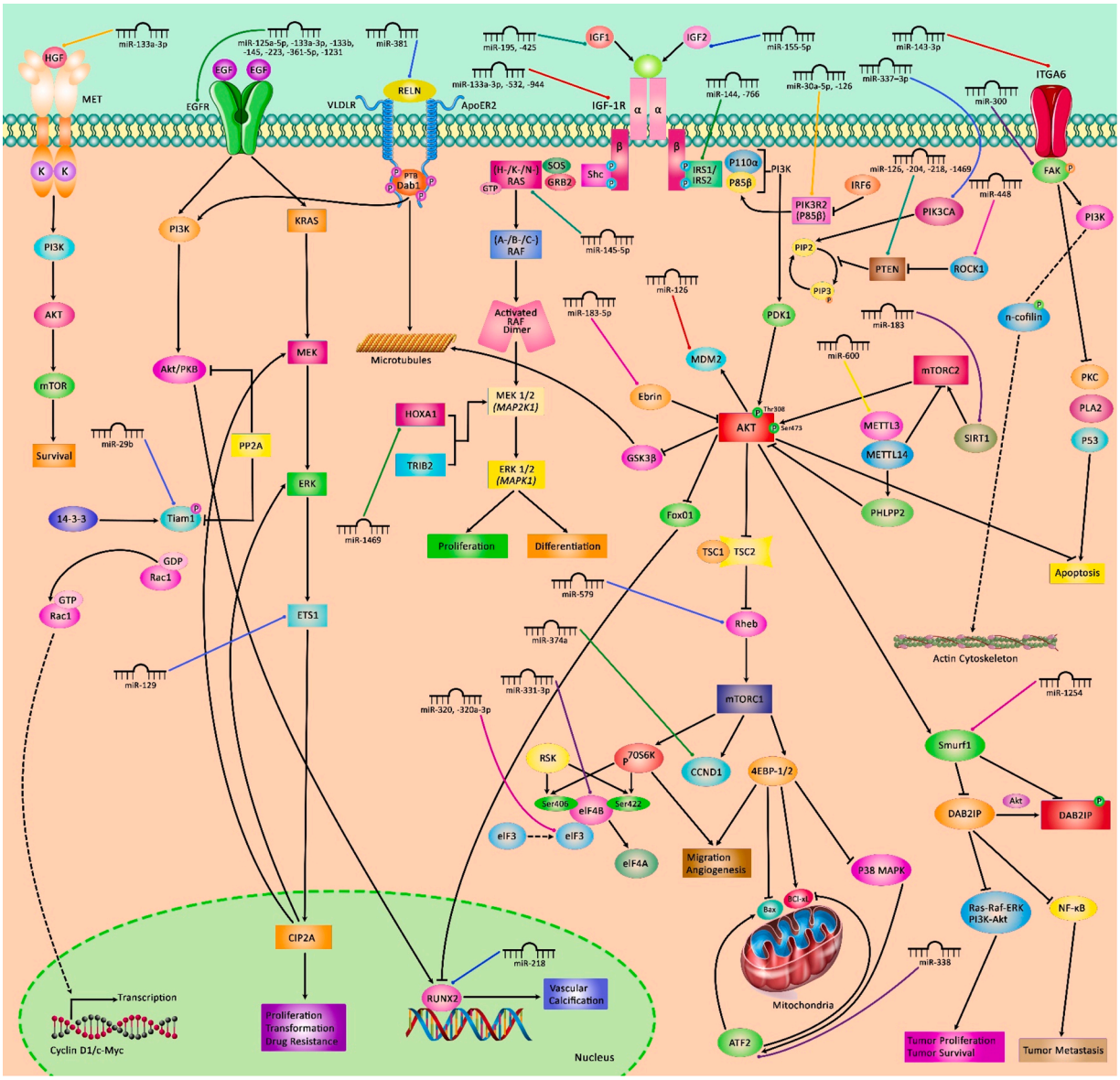

Fig. 2. A diagram of the regulation of PI3K/AKT cascade via miRNAs in various human cancers. Different miRNAs including miR-195, miR-320, miR-425, miR-579, miR-766, and miR-1231 can modulate activity of PI3K/AKT pathway and block carcinogenic processes. These miRNAs have a tumor suppressor role which can impede cell proliferation, migration, and invasion and activate cell apoptosis by modulating their target genes. These miRNAs by directly targeting IGF1, ELF3, Rheb, PDK1, IRS2, and EGFR through the PI3K/AKT pathway can suppress a variety of tumors namely rectal cancer, breast cancer, papillary thyroid carcinoma, melanoma, and glioblastoma [18–24]. Table 1 summarizes the functional data describing the role of tumor suppressor miRNAs which partake in the regulation of PI3K/AKT pathway.

Table 1
The function of tumor suppressor miRNAs in the control of PI3K/AKT pathway in cancer (ANCTs: adjacent non-cancerous tissues).

Cancer Type	microRNA	Role of microRNA	Samples	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
Wilms' Tumor (WT)	miR-155-5p	Tumor Suppressor	87 pairs of WT and ANCTs, 4 WT and 4 uronephrosis blood samples/ GEO and TARGET databases	G401, SKNEP-1, HK-2	IGF2	mTOR	miR-155-5p by targeting IGF2 suppresses cell proliferation, migration, and invasion and promote cell apoptosis in Wilms tumor.	[14]
Bladder Cancer (BCa)	miR-328-3p	Tumor Suppressor	Mouse/human; 28 pairs of BCa and ANCTs	SV-HUC-1, 5637, T24, J82	ITGA5	EMT	miR-328-3p by targeting ITGA5 could inhibit tumorigenesis in BCa via inactivating PI3K/Akt and EMT.	[15]
BCa	miR-125b-5p	Tumor Suppressor	52 pairs of BCa and ANCTs	T24, RT4, J82, 5637, SV-HUC-1	HK2	_	miR-125b-5p by targeting HK2 could suppress BCa cell proliferation and migration and induce apoptosis via the PI3K/Akt pathway.	[16]
BCa	miR-126	Tumor Suppressor	_	BLS	PIK3R2	_	miR-126 by targeting PIK3R2 could enhance apoptosis and inhibit proliferation, migration, and invasion in BCa cells via the PI3K/Akt pathway.	[25]
Nasopharyngeal Carcinoma (NPC)	miR-331-3p	Tumor Suppressor	60 pairs of NPC and ANCTs	NP69, 5-8F, CNE-1	elf4B		miR-331-3p by targeting elf4B impedes proliferation and invasion and promote apoptosis in NPC cells.	[17]
NPC	miR-16	Tumor Suppressor	Mouse/human; 16 NPC and 8 normal NP epithelial tissues	NP69, CNE-1, CNE-2, SUNE-1, C666-1, HNE-1, HONE-1	FGF2	MAPK	miR-16 by targeting FGF2 could inhibit NPC cell proliferation, invasion, and metastasis.	[26]
Retinoblastoma (RB)	miR-936	Tumor Suppressor	Mouse/human; 33 RB and 12 normal retinal tissues	Y79, Werr-RB1, SO-RB50, APRE-19	HDAC9	_	miR-936 by targeting HDAC9 could inhibit RB aggressiveness via deactivating PI3K/Akt pathway.	[27]
RB	miR-448	Tumor Suppressor	21 RB tissues and 7 normal control tissues	Y79, WERI-RB-1, SO-RB50	ROCK1	_	miR-448 by targeting ROCK1 could inhibit the progression of RB.	[28]
Laryngeal Squamous Cell Carcinoma (LSCC)	miR-145	Tumor Suppressor	Mouse	AMC-HN-8	_	_	miR-145 could inhibit tumor growth, invasion, and metastasis in LSCC.	[29]
LSCC	miR-144	Tumor Suppressor	Mouse/human; 24 pairs of LSCC and ANCTs	HEp-2	IRS1	_	miR-144 by targeting IRS1 could suppress tumor growth and metastasis in LSCC cells.	[30]
Esophageal Squamous Cell Carcinoma (ESCC)	miR-133b	Tumor Suppressor	30 pairs of ESCC and ANCTs	KYSE-150, EC109, KYSE-30, Het-1A	EGFR	MAPK/ERK, EMT	miR-133b by targeting EGFR could suppress cell proliferation, migration, and invasion in ESCC cells via inactivating PI3K/Akt and MAPK/ERK signaling pathways.	[31]
Breast Cancer (BC)	miR-1469	Tumor Suppressor	48 pairs of BC and ANCTs, 48 BC blood samples, and 30 healthy blood samples	MCF-10A, MCF-7, MDA-MB-231, SK-BR-3, BT-474	HOXA1, PTEN	Wnt/ β-catenin	miR-1469 by targeting HOXA1 impedes cell proliferation, migration, and invasion and enhance apoptosis via PTEN/ PI3K/Akt and Wnt/β-catenin cascades.	[32]
BC	miR-204	Tumor Suppressor	_	MCF7, CAMA-1, SK-BR-3, BT-20, BT-483, EMT6, Hs 841.T	PTEN	_	miR-204 by targeting PTEN could inhibit proliferation and metastasis in BC.	[33]
BC	miR-320	Tumor Suppressor	Mouse/human; 52 pairs of BC and ANCTs	MCF-7, SK-BR-3, MDA-MB-231, Hs578 T, Hs578Bst	ELF3	EMT	miR-320 by inhibiting ELF3 could suppress the progression of BC cells.	[18]
Triple-Negative Breast Cancer (TNBC)	miR-361-5p	Tumor Suppressor	30 pairs of TNBC and ANCTs	MDA-MB-231	RQCD1, EGFR	_	miR-361-5p by targeting RQCD1 could inhibit migration and invasion in TNBC cells via EGFR/PI3K/Akt pathway.	[34]
Glioma (G)	miR-1231	Tumor Suppressor	Mouse/human; 24 G and 5 normal brain tissues/	U251, LN229, A172, U87, U118, H4, NHAs	EGFR	_	miR-1231 by targeting EGFR could suppress cell	[19]

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	microRNA	Role of microRNA	Samples	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
			CGGA, TCGA, and GSE10611 datasets				proliferation and block cell cycle arrest.	
G	miR-126	Tumor Suppressor	44 G and 20 normal brain tissues	U87MG, NHA	PTEN, MDM2	p53	miR-126 by targeting PTEN and MDM2 could suppress glioma progression through PI3K/Akt and p53 pathways.	[35]
G	miR-489	Tumor Suppressor	Mouse/human; 60 pairs of G and ANCTs	U87, T98, U251, NHA	SPIN1	_	miR-489 by targeting SPIN1 could inhibit proliferation, cell cycle progression, and induce apoptosis in glioma cells.	[36]
Glioblastoma (GBM)	miR-579	Tumor Suppressor	_	A-172, U251, 293 T	Rheb, PDK1	mTOR	miR-579 by targeting Rheb and PDK1could attenuate tumor progression in GBM via PI3K/Akt and mTOR.	[20]
Hepatocellular Carcinoma (HCC)	miR-944	Tumor Suppressor	Mouse/human; 61 pairs of HCC and ANCTs	L02, Hep3B, Bel-7402, SMMC-7721, Huh7, SK-HEP-1	IGF-1R	EMT	miR-944 by targeting IGF-1R could restrict tumor progression, metastasis, and EMT in HCC cells via the PI3K/Akt pathway.	[37]
HCC	miR-300	Tumor Suppressor	110 FFPE HCC tissues, 15 pairs of HCC, and ANCTs	SMMC-7721, LO2, HepG2, Huh7, PLC, MHCC-97 L, HCC-LM3, MHCC-97H	FAK	EMT	miR-300 by targeting FAK affects proliferation, migration, and invasion in HCC cells via regulating PI3K/Akt and EMT.	[38]
HCC	miR-623	Tumor Suppressor	53 pairs of HCC and ANCTs	Hep3B, 7721, Huh7, HepG2, Bel-7402	XRCC5	Wnt/ β-catenin, ERK/JNK	miR-623 by targeting XRCC5 could suppress the progression and metastasis of HCC.	[39]
HCC	miR-1296	Tumor Suppressor	Mouse/human; 126 pairs of HCC and ANCTs	MHCC-97 L, HCCLM3, MHCC-97H, Huh7, Hep3B, LO2	SRPK1	EMT	miR-1296 by targeting SRPK1 could suppress tumor growth and EMT via the PI3K/Akt pathway.	[40]
Acute Myeloid Leukemia (AML)	miR-345-5p	Tumor Suppressor	29 AML blood samples, 29 healthy blood samples	K562, healthy human bone marrow monocytes	AKT2	_	miR-345-5p by targeting AKT2 could regulate proliferation and cell cycle and facilitate apoptosis in AML cells via the PI3K/Akt pathway.	[41]
AML	miR-139-5p	Tumor Suppressor	51 AML BM samples, 21 healthy BM samples	THP-1, KG-1a, OCI-AML3, U937, HL-60, HS-5, 293 T	Tspan3	_	miR-139-5p by targeting Tspan3 inhibits leukemogenesis in AML cells through PI3K/Akt pathway.	[42]
AML	miR-183-5p	Tumor Suppressor	Mouse/human; 7 BM samples and 30 blood samples from AML patients, 2 BM samples and 10 blood samples as healthy controls	THP-1, HL-60, U937, NB-4, SHI-1	Erbin	RAS/RAF/ MEK/ERK	miR-183-5p by regulating Erbin could enhance the proliferation of AML cells through induction of RAS/RAF/MEK/ERK and PI3K/Akt/FoxO3a pathways.	[43]
Ewing's Sarcoma	miR-185	Tumor Suppressor	_	RD-ES, A673, SK-ES-1, SCCH	E2F6	Wnt/ β-catenin, mTOR	miR-185 by targeting E2F6 could suppress the progression of Ewing's sarcoma via inhibiting PI3K/Akt/mTOR and Wnt/β-catenin pathways.	[44]
Ewing's Sarcoma	miR-30d	Tumor Suppressor	_	SK-ES-1	_	MEK/ERK	miR-30d could inhibit cell progression in Ewing's sarcoma by inhibiting MEK/ERK and PI3K/Akt pathways.	[45]
Ovarian Cancer (OC)	miR-337–3p	Tumor Suppressor	Mouse/human; 105 EOC tissues and 51 normal ovarian tissues	293 T, A2780, SKOV-3, OVCAR-3, ES-2, OV-90, HOSEpiC, CAOV-3	PIK3CA, PIK3CB	_	miR-337-3p by targeting PIK3CA and PIK3CB could suppress the proliferation of EOC cells.	[46]
OC	miR-149	Tumor Suppressor	72 pairs of OC and ANCTs	SKOV3, OVCAR3, HO8910, A2780, IOSE29	MSI2	EMT	miR-149 by targeting MSI2 could inhibit OC cell growth and metastasis via regulating EMT and PI3K/Akt pathways.	[47]
Endometrial Cancer (EC)	miR-101	Tumor Suppressor	37 EC and 22 normal control tissues	HEC-1A, HEEC	_	mTOR	miR-101 could reduce cell proliferation and invasion and enhance apoptosis in endometrial neoplasm.	[48]
Cervical Cancer (CC)	miR-149	Tumor Suppressor	Mouse/human; a number of CC and matched normal tissues	HeLa, SiHa, Me180, HcerEpic	GIT1	mTOR	miR-149 by targeting GIT1 could inhibit proliferation and enhance apoptosis in cervical cancer via the PI3K/Akt pathway.	[49]

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	microRNA	Role of microRNA	Samples	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
CC	miR-383	Tumor Suppressor	115 pairs of CC and ANCTs	HeLa, SiHa, CaShi, C4-1	PARP2	mTOR	miR-383 by targeting PARP2 could inhibit proliferation, migration, and invasion in cervical cancer cells.	[50]
CC	miR-99b	Tumor Suppressor	132 pairs of CC and ANCTs	HeLa, SiHa, CaShi, C4-1	_	mTOR	miR-99b could inhibit cell proliferation and invasion.	[51]
CC	miR-125a-5p	Tumor Suppressor	Mouse/human; 20 pairs of CC and ANCTs	HeLa, Caski	GALNT7, EGFR	_	miR-125a-5p by inhibiting GALNT7 and EGFR could attenuate cell proliferation and invasion in CC cells.	[52]
CC	miR-338	Tumor Suppressor	30 pairs of CC and ANCTs	Siha, HeLa, C33A, Me180	ATF2	mTOR	miR-338 by targeting ATF2 could inhibit proliferation and autophagy in CC cells via PI3K/Akt/mTOR signaling pathway.	[53]
CC	miR-204	Tumor Suppressor	Mouse/human; 30 pairs of CC and ANCTs	HeLa, C33A, SiHa, MS751, HCC94, CaSki, Ect1/E6E7	EphB2	_	miR-204 by targeting EphB2 could suppress migration, invasion, and metastasis and induce apoptosis in CC.	[54]
Gallbladder Cancer (GBC)	miR-143-3p	Tumor Suppressor	Mouse/human; 49 pairs of GBC and ANCTs	GBC-SD, SGC996, NOZ, OCUG-1, EHGB-1, HMVECs	ITGA6, STAT3	_	miR-143-3p by targeting ITGA6 could suppress tumor growth and PLGF-induced angiogenesis in GBC via PI3K/Akt/STAT3 signaling.	[55]
Liver Cancer	miR-30a-3p	Tumor Suppressor	_	HepG2, L02	DNMT3a	_	miR-30a-3p by targeting DNMT3a could inhibit the proliferation of liver cancer cells.	[56]
Prostate Cancer (PCa)	miR-129	Tumor Suppressor	Mouse/human; 30 pairs of PCa and ANCTs	LNCap, PC-3, DU-145, RPWE-1	ETS1	mTOR, EMT	miR-129 by targeting ETS1 could inhibit cell proliferation, metastasis, and EMT.	[57]
PCa	miR-188-5p	Tumor Suppressor	Mouse/human; 180 pairs of PCa and ANCTs	PC-3, LNCaP	LAPTM4B	_	miR-188-5p by targeting LAPTM4B could attenuate cell proliferation, migration, and invasion and enhance apoptosis in PCa.	[58]
PCa	miR-133a-3p	Tumor Suppressor	Mouse/human; 225 prostate adenocarcinoma patients, 20 pairs of PCa and ANCTs, 48 benign prostate lesions/ TCGA dataset	22RV1, PC-3, VCaP, DU145, LNCaP, RWPE-1, C4-2B	EGFR, FGFR1, IGF1R, MET	_	miR-133a-3p by affecting several cytokine receptors inhibits bone metastasis via inactivating the PI3K/Akt axis.	[59]
PCa	miR-381	Tumor Suppressor	Mouse	PC3, DU145, LNCaP, PWPE-1	RELN	mTOR, autophagy	miR-381 by targeting RELN could facilitate autophagy and apoptosis in PCa cells via PI3K/Akt/mTOR pathway.	[60]
Papillary Thyroid Carcinoma (PTC)	miR-29a	Tumor Suppressor	Mouse/human; 30 pairs of PTC and ANCTs	K1	AKT3	_	miR-29a by targeting AKT3 impedes proliferation, migration, and invasion and induces apoptosis in PTC.	[61]
PTC	miR-218	Tumor Suppressor	Mouse/human; 21 pairs of PTC and ANCTs	TPC-1, K-1, Nthy-ori3-1	Runx2, PTEN	_	miR-218 by targeting Runx2 could suppress cell viability, invasion, and induce apoptosis in PTC via inactivation of PTEN /PI3K/Akt pathway.	[62]
PTC	miR-766	Tumor Suppressor	Mouse/human; 47 pairs of PTC and ANCTs	HT-ori3, HTH83, TPC-1, BCPAP	IRS2	_	miR-766 by targeting IRS2 could inhibit PTC progression, migration, and invasion via the PI3K/Akt pathway.	[21]
Lung Cancer	miR-126	Tumor Suppressor	_	SPC-A1, LLC	Snail	EMT	miR-126 could suppress EMT and metastasis.	[63]
Lung Cancer	miR-600	Tumor Suppressor	_	A549, H1299	METTL3	β-catenin	miR-600 by targeting METTL3 could enhance apoptosis and inhibit lung cancer progression.	[64]
Lung Adenocarcinoma (LA)	miR-381	Tumor Suppressor	Mouse/human; 54 pairs of LA and ANCTs	A549, SPC-A1, H1299, PC-9, BEAS–2B	LMO3	EMT	miR-381 by targeting LMO3 could inhibit LA cell biological progression via regulating EMT and PI3K/Akt pathways.	[65]
Non-Small Cell Carcinoma (NSCLC)	miR-30a-5p	Tumor Suppressor	_	NCI-H460, NCI-H1975	PIK3R2	_	miR-30a-5p by reducing PIK3R2 could induce cell apoptosis and inhibit invasion and migration in NSCLC cells.	[66]
NSCLC	miR-101-3p	Tumor Suppressor	Mouse	H1299, SPC-A-1, A549, H460, H520, MRC-5	MALAT-1	_	miR-101-3p by targeting MALAT-1could inhibit growth and metastasis of NSCLC cells.	[67]

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	microRNA	Role of microRNA	Samples	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
NSCLC	miR-409	Tumor Suppressor	Mouse/human; 85 pairs of NSCLC and ANCTs	A549, H460	SPIN1	_	miR-409 by targeting blocks proliferation, migration, and invasion.	[68]
NSCLC	miR-874	Tumor Suppressor	Mouse/human; 49 pairs of NSCLC and ANCTs	A549, H1299, BEAS-2B	AQP3	EMT	miR-874 by inhibiting AQP3 could attenuate cell proliferation, mobility, and EMT in NSCLC cells.	[69]
NSCLC	miR-145	Tumor Suppressor	NSCLC tissues and blood samples (n = 6), healthy tissues and blood samples as control (n = 6)	A549	EGFR	_	miR-145 by targeting EGFR could inhibit migration and induce apoptosis in NSCLC cells.	[70]
NSCLC	miR-320a-3p	Tumor Suppressor	Mouse/human; 80 pairs of NSCLC and ANCTs	Calu-3, H1299, A549, SK-MES-1, BEAS-2B	ELF3	_	miR-320a-3p by targeting ELF3 could inhibit cell metastasis and invasion in NSCLC cells.	[71]
NSCLC	miR-496	Tumor Suppressor	35 pairs of NSCLC and ANCTs	H1650, H292, H1944, A549, EBAS-2B	BDNF	_	miR-496 by targeting BDNF could suppress tumorigenesis via PI3K/Akt signaling pathway in NSCLC.	[72]
NSCLC	miR-223	Tumor Suppressor	6 NSCLC and 6 healthy blood samples	A549	EGFR	_	miR-223 by targeting EGFR could increase apoptosis and suppress tumor progression of NSCLC through the PI3K/Akt pathway.	[73]
Melanoma	miR-425	Tumor Suppressor	15 pairs of melanoma tissues and ANCTs	SK-MEL-28, UACC257, A375, WM-115, NHEM	IGF-1	_	miR-425 by targeting IGF-1 could inhibit cell proliferation and metastasis in melanoma.	[22]
Melanoma	miR-145-5p	Tumor Suppressor	Mouse/human; 83 pairs of melanoma and ANCTs	293 T, SK-mel-28, VMM917, NHEMs	NRAS	MAPK	miR-145-5p by targeting NRAS could attenuate cell proliferation, migration, and invasion and enhance apoptosis in melanoma.	[74]
Rectal Cancer	miR-195	Tumor Suppressor	_	SW837, SW1463, Human rectal mucosa epithelial cell line	IGF1	_	miR-195 by targeting IGF1 could attenuate tumor progression in rectal cancer via the PI3K/Akt pathway.	[23]
Colon Cancer	miR-374a	Tumor Suppressor	Mouse/human; 90 pairs of colon cancer and ANCTs	HCT116, SW620, SW480	CCND1	EMT	miR-374a by targeting CCND1could suppresses proliferation, migration, invasion, and intrahepatic metastasis via inactivating PI3K/Akt pathway.	[75]
Colorectal Cancer (CRC)	miR-29b	Tumor Suppressor	24 pairs of CRC and ANCTs	HT29, HCT116, SW480, SW620, SW480/M5, NCM460	Tiam1	EMT	miR-29b by targeting Tiam1 could decrease tumor growth, metastasis and EMT via PI3K/Akt pathway.	[76]
CRC	miR-1	Tumor Suppressor	Mouse/human; 24 pairs of CRC and ANCTs	HT29, HCT116, SW480, SW620	LASP1	MAPK, EMT, ERK	miR-1 by targeting LASP1 could reduce EMT, metastasis, and tumor growth.	[77]
CRC	miR-532	Tumor Suppressor	Mouse/human; 58 pairs of CRC and ANCTs	SW480, SW620, HCT116, HT29	IGF-1R	_	miR-532 by targeting IGF-1R could suppress proliferation, migration, and invasion in CRC cells.	[78]
Gastric Cancer (GC)	miR-489	Tumor Suppressor	52 pairs of GC and ANCTs	SGC-7901, MKN45, GES-1	HDAC7	EMT	miR-489 by inhibiting HDAC7 could suppress GC cell proliferation, invasion, and migration.	[79]
GC	miR-107	Tumor Suppressor	Mouse	SGC-7901, MKN-45, KATO III, BGC-823, AGS, MKN-28, MKN1, GES-1	BDNF	_	miR-107 by targeting BDNF could inhibit GC cell proliferation and metastasis.	[80]
GC	miR-1236-3p	Tumor Suppressor	83 pairs of GC and ANCTs	MKN-45, SGC-7901, MGC-803, GES-1	MTA2	EMT	miR-1236-3p by targeting MTA2 could inhibit proliferation, invasion, and metastasis and suppress EMT in GC via the PI3K/Akt pathway.	[81]
GC	miR-137	Tumor Suppressor	Mouse/human; 107 pairs of GC and ANCTs	MGC-803, HGC-27, MKN-45, SGC-7901	Cox-2	_	miR-137 by targeting Cox-2 could inhibit tumor growth in GC.	[82]
GC	miR-183	Tumor Suppressor	20 pairs of GC and ANCTs	GES-1, BGC-823, SGC-7901, HGC-27	SIRT1, MALAT1	mTOR, autophagy	MALAT1/miR-183 by targeting SIRT1could attenuate GC development and	[83]

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	microRNA	Role of microRNA	Samples	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
							enhance apoptosis and autophagy via PI3K/Akt/ mTOR pathway.	
GC	miR-1254	Tumor Suppressor	Mouse/human; 90 pairs of GC and ANCTs	SGC7901, BGC823, MKN45, HGC27, MGC803, GES-1	Smurf1	EMT	miR-1254 by targeting Smurf1 could suppress proliferation, migration, invasion, and EMT in GC.	[84]
GC	miR-183	Tumor Suppressor	TCGA dataset	AGS, MKN-45	TCF12	_	miR-183 by targeting TCF12 could enhance apoptosis and inhibit proliferation, migration, and invasion in GC.	[85]

rate of distant or regional metastasis, and larger tumor size. Functional assays have demonstrated the role of this miRNA in the suppression of bladder cancer cell viability and migration and induction of apoptosis through inactivation of the PI3K/AKT pathway [16]. miR-331-3p has been displayed to be down-regulated in nasopharyngeal carcinoma tissues and cell lines. This miRNA impedes proliferation and invasion of nasopharyngeal carcinoma cells and enhances cell apoptosis via decreasing elF4B and subsequent inhibition of the phosphorylation of PI3K and AKT [17]. Fig. 2 illustrates the modulation of PI3K/AKT signaling pathway by various tumor suppressor miRNAs in different human cancers.

4. Up-regulated PI3K/AKT-associated miRNAs in cancers

Also, several oncogenic miRNAs accomplish their function through increasing activity of the PI3K/AKT pathway. For instance, miR-182 and miR-135b are up-regulated in colorectal cancer sections compared with the corresponding noncancerous tissues. ST6GALNAC2 has been identified as the direct target of these miRNAs. miR-182/-135b also enhances the activity of the PI3K/AKT pathway. Therefore, the miR-182/-135b/ST6GALNAC2/PI3K/AKT axis has been proposed as a potential biomarker and therapeutic candidate in colorectal cancer patients [86]. Moreover, expression of miR-182 has been lower in postoperative serum specimens from patients with colorectal cancer, compared with preoperative serum specimens from these patients. Expression of this miRNA was further increased in serum samples of patients whose disorder recurred. Over-expression of this miRNA enhances cell proliferation, colony formation, augmented ki67 expression, and increased the invasiveness of cancer cells by up-regulating MMP-2 and MMP-9 expressions. In addition, miR-182 binds with the 3' UTR of DAB2IP and inhibits its expression. Thus, miR-182 acts as an oncogenic miRNA in colorectal cancer cells by affecting expression of DAB2IP, which possibly contributes to the induction of the PI3K/Akt/mTOR and Wnt/β-catenin [87]. Expression of miR-193 has been elevated in triple-negative breast neoplasm compared with non-tumor tissues and normal cell lines. Over-expression of this miRNA was associated with the poor prognosis of these patients. Mechanistically, this miRNA enhances cell proliferation and invasion through binding with the 3' UTR of ING5 and modulating PI3K/AKT signaling pathway. miR-193 silencing suppresses cell invasion-mediated EMT as well [88]. Table 2 shows the function of oncomiRs in the regulation of the PI3K/AKT pathway.

5. Diagnostic impact of PI3K/AKT-associated miRNAs

Expression levels of PI3K/AKT-associated miRNAs are potential diagnostic markers in cancer patients. For instance, expression of the down-regulated miRNA, miR-337–3p can distinguish disease status in epithelial ovarian cancer tissues with an accuracy of 0.74 [46]. Besides, expression levels of these miRNAs can predict the survival of cancer patients. For example, down-regulation of miR-125b-3p, miR-320, miR-126, and miR-149 were associated with poor survival times of patients with bladder cancer, breast cancer, glioma, and ovarian cancer, respectively [16,18,35,47]. On the other hand, over-expression of miR-494-3p was associated with poor relapse-free survival and overall survival of patients with hepatocellular carcinoma [97]. Table 3 displays the results of studies that appraised the prognostic roles of PI3K/AKT-associated miRNAs in cancers.

6. LncRNAs and PI3K/AKT pathway

The functional link between dysregulation of lncRNAs and activation of PI3K/AKT pathway has been appraised in numerous studies.

7. Down-regulated PI3K/AKT-associated lncRNAs in cancers

Yao et al. have demonstrated down-regulation of lncRNA in osteosarcoma cell lines and clinical samples. Functional studies revealed the role of this lncRNA in inhibition of cell proliferation and induction of apoptosis in a certain osteosarcoma cell line. Subsequent in silico and functional investigations demonstrated the impact of lncRNA 691 in the suppression of expression of miR-9-5p. Notably, PTEN has been shown to be a direct target of miR-9-5p. Thus, lncRNA 691/miR-9-5p can modulate the PTEN/PI3K/AKT pathway in osteosarcoma through regulation of PTEN expression [124]. Cao et al. have shown down-regulation of lncRNA ADAMTS9-AS2 in gastric cancer in association with poor patients' outcomes. The functional studies revealed the role of ADAMTS9-AS2 in inhibition of gastric cancer cell proliferation, suppression of migration and invasion, and activation of apoptosis through modulation of PI3K/Akt pathway [125]. Luo et al. have displayed under-expression of TCL6 in hepatocellular carcinoma (HCC) tissues compared with control samples. In HCC cell lines, the down-regulation of this lncRNA was accompanied by the up-regulation of miR-106a-5p. TCL6 has been shown to suppress cell proliferation, migration, and invasion of HCC cells through binding with miR-106a-5p and releasing PTEN from its inhibitory effects. miR-106a-5p silencing or TCL6 up-regulation enhanced the protein level of PTEN and inhibited phosphorylation of AKT and expression of PI3K protein [126]. Zhang et al. have detected decreased levels of LINC00982 in renal cancer samples compared with the adjacent non-cancerous tissues in association with tumor size and TNM stage. Over-expression of LINC00982 suppressed cell proliferation and enhanced apoptosis in renal cancer cell lines through modulation of PI3K/AKT activity [127]. Table 4 provides

Table 2
The function of oncogenic miRNAs on PI3K/AKT pathway in cancer (ANCTs: adjacent non-cancerous tissues).

Cancer type	microRNA	Role of microRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
Colorectal Cancer (CRC)	miR-182/-135b	Oncogene	Mouse/human; 33 pairs of CRC and ANCTs	FHC, SW480, SW620	ST6GALNAC2	_	miR-182/-135b by targeting ST6GALNAC2 could enhance proliferation, migration, and invasion.	[86]
CRC	miR-182	Oncogene	Mouse/human; blood samples (CRC, n = 57), (healthy, n = 28), 25 pairs of CRC and ANCTs	FHC, SW480, LoVo, HCT116, Caco-2, SW620	DAB2IP	Wnt/ β-catenin, mTOR	miR-182 by targeting DAB2IP regulates cell proliferation, invasion, and tumor growth in CRC via regulating PI3K/Akt/ mTOR and Wnt/β-catenin cascades.	[87]
CRC	miR-106a	Oncogene	40 pairs of CRC and ANCTs	NCM640, SW620, HT29	PTEN	_	miR-106a by targeting PTEN could increase cell proliferation and inhibit apoptosis in CRC cells via the PI3K/Akt pathway.	[89]
Triple-Negative Breast Cancer (TNBC)	miR-193	Oncogene	Mouse/human; 50 pairs of TNBC and ANCTs	MDA-MB-231, BT483, MCF-10A	ING5	EMT	miR-193 by targeting ING5 could confer cell proliferation and invasion in TNBC cells.	[88]
TNBC	miR-214	Oncogene	37 TNBC, 37 healthy control, 37 non-TNBC BCa	MDA-MB-231	α1-AT	mTOR	miR-214 by targeting α1-AT via PI3K/Akt/mTOR pathway could enhance proliferation, migration, and invasion in TNBC cells.	[90]
Breast Cancer (BC)	miR-106b, miR-93	Oncogene	36 pairs of BC and ANCTs	MCF-10A, MCF-7, MDA-MB-231	PTEN		miR-106b and miR-93 by targeting PTEN could enhance cell proliferation, migration, and invasion in BC cells.	[91]
Bladder Cancer (BCa)	miR-21	Oncogene	_	T24, THP-1	PTEN, STAT3	-	miR-21 by inhibiting PTEN could active M2-type related genes in macrophages to enhance the invasion and migration of BCa cells via enhancing PI3K/Akt-induced STAT3 signaling activity.	[92]
BCa	miR-103/ 107	Oncogene	17 pairs of BCa and ANCTs	UMUC2, 5637	PTEN	_	miR-103/107 by targeting PTEN could induce tumorigenicity in BCa cells via activating PI3K/Akt pathway.	[93]
Liver Cancer	miR-21-3p	Oncogene	Mouse	PLC, HepG2, Huh7, LO2	PTEN, BAD	_	miR-21-3p by targeting PTEN could attenuate TRAIL-mediated apoptosis in liver cancer stem cells.	[94]
Hepatocellular Carcinoma (HCC)	miR-616	Oncogene	123 pairs of HCC and ANCTs	HepG2, THLE-3	PTEN	_	miR-616 by targeting PTEN could contribute to malignant progression of HCC via activating PI3K/Akt pathway.	[95]
HCC	miR-367	Oncogene	126 pairs of HCC and ANCTs	HepG2, THLE-3	PTEN	_	miR-367 by targeting PTEN could contribute to malignant progression of HCC via PI3K/Akt pathway.	[96]
HCC	miR-494-3p	Oncogene	Mouse/human; 271 pairs of HCC and ANCTs	SMMC-7721, Huh7, HCC-LM3, HepG2, Hep3B, THLE-3	PTEN	_	MiR-494-3p by targeting PTEN could enhance proliferation, invasion, and metastasis in HCC cells.	[97]
HCC	miR-3691-5p	Oncogene	43 pairs of HCC and ANCTs, TCGA dataset	293 T, Hep3B, SMMC-7721, MHCC97-L, MHCC97-H, HCCLM3, L02	PTEN	_	miR-3691-5p by regulating PTEN could promote HCC cell migration and invasion through activating PI3K/Akt pathway.	[98]
HCC	miR-106b-5p	Oncogene	Mouse/human; 20 pairs of HCC and ANCTs	MHCC97 L, MHCC97H, HCCLM3, Bel-7402, PLC/5, chang liver	PTEN	_	miR-106b-5p by targeting PTEN increases HCC stemness maintenance and metastasis.	[99]
HCC	miR-221	Oncogene	_	PLC/PRF/5, Huh7, HepG2, SNU-449, SNU-423, SK-Hep-1	CD44	mTOR	miR-221 by targeting CD44 could confer tumor growth in HCC via PI3K/Akt/mTOR pathway.	[100]
Laryngeal Squamous Cell Carcinoma (LSCC)	miR-17-5p	Oncogene	Mouse/human; 39 pairs of LSCC and ANCTs	HEp-2, SCC-2, SCC-40, HOK	PIK3R1	_	miR-17-5p by targeting PIK3R1 could participate in LSCC cell proliferation and apoptosis via deactivating PI3K/Akt pathway.	[101]
Osteosarcoma (OS)	miR-191-5p	Oncogene	Mouse/human; 63 pairs of OS and ANCTs	U2OS, MG63, Saos2, hFOB1.19	EGR1	EMT	miR-191-5p by inhibiting EGR1 could promote cell proliferation, migration, and invasion in OS via EMT and PI3K/Akt signaling pathways.	[102]
Lung Cancer	miR-200	Oncogene			FOG2	_		[103]

(*continued on next page*)

Table 2 (*continued*)

Cancer type	microRNA	Role of microRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
			33 pairs of lung cancer and ANCTs	HCC827zeb1, 344SQ			miR-200 by targeting FOG2 could promote lung cancer cell growth.	
Non-Small Cell Carcinoma (NSCLC)	miR-4286	Oncogene	31 pairs of NSCLC and ANCTs	A549, SPC-A1, H1299, H460, H226,H1975	PTEN	_	miR-4286 by targeting PTEN could promote cell proliferation, migration, and invasion.	[104]
NSCLC	miR-21	Oncogene	Mouse	HBE, A549	ASPP2	NF-κB, EMT	miR-21 by targeting ASPP2 could inhibit apoptosis and induce cell migration, invasion, and EMT in NSCLC cells via PI3K/Akt and NF-κB cascades.	[105]
Gastric Cancer (GC)	miR-107	Oncogene	Mouse/human; 150 pairs of GC and ANCTs	GES-1, AGS, KATO-III, MGC-803, MKN-45, MKN-28, HGC27, NS-3	FAT4	EMT	miR-107 by targeting FAT4 could promote proliferation, migration invasion, and tumorigenicity in GC cells via regulating EMT and PI3K/Akt pathways.	[106]
GC	miR-21	Oncogene	_	MKN74	PTEN	mTOR	miR-21 by targeting PTEN could increase cell proliferation, migration, and invasion in GC cells via PI3K/Akt/mTOR.	[107]
GC	miR-28	Oncogene	31 pairs of GC and ANCTs	SGC-7901, MGC-803, MKN-1, BGC-823, AGS	PTEN	_	miR-28 by targeting PTEN enhances cell proliferation and invasion.	[108]
GC	miR-592	Oncogene	Mouse/human; 70 pairs of GC and ANCTs	SGC7901, BGC823, MGC803, AGS, GES-1	Spry2	MAPK/ERK, EMT	MiR-592 by targeting Spry2 could promote GC proliferation, migration, and invasion and induce EMT.	[109]
Uveal Melanoma (UM)	miR-222	Oncogene	Mouse	C918, MUM-2B	_	_	HMGA1/miR-222 axis could promote cell proliferation, migration, and tumor progression in UM via PI3K/Akt/MMP-9 signaling pathway.	[110]
Retinoblastoma (RB)	miR-182	Oncogene	Mouse/human; 22 RB and 34 normal retinal tissues	Y79, WERI-Rb-1	CADM2	_	miR-182 by targeting CADM2 could promote cell viability, invasion, and angiogenesis in RB.	[111]
Diffuse Large B-Cell Lymphoma (DLBCL)	miR-21	Oncogene	200 FFPE DLBCL tissues	OCILy1, OCI-Ly2, SU-DHL4, SU-DHL5, SU-DHL8, OCI-Ly10, SU-DHL9	FOXO1, PTEN	mTOR	miR-21 by targeting FOXO1 and PTEN could inhibit proliferation, migration, and invasion in DLBCL.	[112]
Melanoma	miR-25	Oncogene	_	M14, A875, MV3, uacc257, HEM-a	RBM47	mTOR	miR-25 by targeting RBM47 could promote melanoma progression via PI3K/Akt/mTOR pathway.	[113]
Multiple Myeloma (MM)	miR-451	Oncogene	Mouse	NCI-H929, RPMI8226, KMS-11, LP-1, U266, SKO	TSC1	mTOR	miR-451 by targeting TSC1 could regulate the stemness of side population cells in MM.	[114]
MM	miR-20a	Oncogene	30 MM plasma samples, 8 healthy plasma samples	MM1S, U266, RPMI-8226, nPCs	PTEN	_	miR-20a by targeting PTEN could enhance cell proliferation and migration and suppress apoptosis in MM.	[115]
Esophageal Squamous Cell Carcinoma (ESCC)	miR-18a	Oncogene	_	TE13, Eca109	PTEN, Cyclin D1	mTOR	miR-18a by suppression of PTEN increases expression of Cyclin D1 thus promoting the cell cycle progression of ESCC cells via PI3K/Akt/mTOR pathway.	[116]
ESCC	miR-214	Oncogene	Mouse/human; 30 pairs of ESCC and ANCTs	KYSE150, ECA-109, KYSE450, HET-1A	LZTS1	mTOR	miR-214 by targeting LZTS1 could promote cell metastasis and inhibit apoptosis in ESCC cells.	[117]
Nasopharyngeal Carcinoma (NPC)	miR-144-3p	Oncogene	Mouse/human; 265 NPC tissues (184 EBV positive, 81 EBV negative), 36 non-NPC tissues	CNE1, CNE2, C666-1, HONE1, HNE1, 293 T	PTEN	EMT	miR-144-3p by targeting PTEN could compel EMT and facilitate NPC via PI3K/Akt pathway.	[118]
NPC	miR-155	Oncogene	_	CNE2	PTEN	_	miR-155 by targeting PTEN could promote proliferation and inhibit apoptosis in NPC cells.	[119]
Pituitary Adenoma	miR-106b	Oncogene	55 pituitary adenoma tissues and 8 normal pituitary tissues	AtT-20	PTEN	_	miR-106b by targeting PTEN could promote cell proliferation and invasion.	[120]
Follicular Thyroid Carcinoma (FTC)	miR-146a/b	Oncogene	Mouse/human; 110 FTC tissues and 110 normal thyroid tissues	FTC-133, FTC-238, Nthy-ori 3-1	ST8SIA4	mTOR	miR-146a/b by targeting ST8SIA4 could promote proliferation, migration and invasion in FTC cells via PI3K/Akt/mTOR signalling pathway.	[121]
	miR-34a	Oncogene		TPC-1	GAS1, Bad	_		[122]

(*continued on next page*)

Table 2 (*continued*)

Cancer type	microRNA	Role of microRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
Papillary Thyroid Carcinoma (PTC)			25 pairs of PTC and ANCTs				miR-34a by targeting GAS1 could promote cell proliferation and inhibit apoptosis in PTC cells.	
Ovarian Cancer (OC)	miR-21	Oncogene	_	IOSE80, A2780, SKOV-3	PTEN	_	miR-21 by targeting PTEN could contribute to the progression of OC.	[123]

the brief summary of the effects of tumor suppressor lncRNAs in the regulation of the PI3K/AKT pathway in cancer.

8. Up-regulated PI3K/AKT-associated lncRNAs in cancers

Several oncogenic lncRNAs accomplish their carcinogenic effects through activation of the PI3K/AKT pathway. For instance, Wang et al. have shown up-regulation of lncRNA RP1-93H18.6 in cervical cancer cells and tissues. This lncRNA has been shown to enhance the activity of the P13K/AKT pathway. Functional and in vivo studies indicated that inhibition of lncRNA RP1-93H18.6 attenuated the initiation and progression of cervical cancer via blocking the PI3K/AKT pathway [146]. Qu et al. have reported up-regulation of HOXA-AS2 in acute myeloid leukemia (AML) patients in correlation with greater white blood cell and bone marrow blast counts, unfavorable cytogenetic abnormalities, more quantifiable residual disease positivity, and poor prognosis. Moreover,

Table 3
Prognostic role of PI3K/AKT-associated miRNAs in cancers.

Sample Number	Kaplan-Meier Analysis	Univariate Cox Regression	Multivariate Cox Regression	Refs.
52 BCa patients	Low amounts of miR-125b-5p were associated with shorter OS.	-	-	[16]
52 GC patients	Low amounts of miR-489 were associated with poorer OS and PFS.	-	-	[79]
72 OC patients	Low amounts of miR-149 were associated with shorter OS.	-	-	[47]
49 NSCLC patients	Low amounts of miR-874 were associated with shorter OS.	-	-	[69]
50 TNBC patients	High amounts of miR-193 were associated with shorter OS.	-	-	[88]
52 BC patients	Low amounts of miR-320 were associated with shorter OS.	-	-	[18]
39 LSCC patients	High amounts of miR-17-5p were associated with sorter OS.	-	-	[101]
44 glioma patients	Low amounts of miR-126 were associated with shorter OS.	-	-	[35]
63 OS patients	High amounts of miR-191-5p were associated with shorter OS.	-	-	[102]
28 BCa patients	Low amounts of miR-328-3p were associated with shorter OS.	-	-	[15]
54 LA patients	Low amounts of miR-381 were associated with shorter OS.	-	-	[65]
369 HCC patients from TCGA dataset	High amounts of miR-3691-5p were associated with shorter OS.	-	-	[98]
61 HCC patients	Low amounts of miR-944 were associated with shorter DFS and OS.	-	-	[37]
110 HCC patients	Low amounts of miR-300 were associated with shorter OS and DFS.	Low expression of miR-300 was correlated with advanced Edmondson-Steiner grades.	Low expression of miR-300 was correlated with tumor number, vascular invasion, and advanced BCLC stage.	[38]
223 PCa from TCGA dataset	Low amounts of miR-133a-3p were associated with shorter bone metastasis-free survival and PFS.	-	Low expression of miR-133a-3p was correlated with lymph node involvement.	[59]
85 NSCLC patients	Low amounts of miR-409 were associated with shorter OS and DFS.	-	-	[68]
271 HCC patients	High expression of miR-494-3p were associated with shorter RFS and OS.	-	-	[97]
49 GBC patients	Low amounts of miR-143-3p were associated with shorter OS.	-	-	[55]
126 HCC patients	Low amounts of miR-1296 were associated with shorter OS and DFS.	-	-	[40]
60 glioma patients	Low amounts of miR-489 were associated with shorter OS.	-	Low amounts of miR-489 were correlated with advanced WHO grades.	[36]
90 colon cancer patients	Low amounts of miR-374a were associated with shorter OS.	-	Low amounts of miR-374a were correlated with lymph node involvement.	[75]
200 DLBCL patients	High amounts of miR-21 were associated with shorter OS.	-	High amounts of miR-21 were correlated with poor R-IPI index.	[112]

Table 4
The function of tumor suppressor lncRNAs in the regulation of PI3K/AKT pathway in cancer (ANCTs: adjacent non-cancerous tissues).

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Assessed Cell line	Targets/ Regulators	Additional pathway	Function	Refs.
Osteosarcoma (OS)	691	Tumor Suppressor	17 pairs of OS and ANCTs	MG-63, U2OS, 143B, hFOB 1.19	miR-9-5p, PTEN	_	LncRNA 691 by targeting miR-9-5p could inhibit cell viability, proliferation, and promote apoptosis in OS cells.	(124)
OS	GAS5	Tumor Suppressor	Mouse/ human; 20 pairs of OS and ANCTs	hFOB1.19, Saos2, 143B, MG-63, U2OS, HOS	miR-23a-3p, PTEN	_	GAS5 by targeting miR-23a-3p could suppress proliferation and invasion of OS cells via PTEN/ PI3K/Akt axis.	(128)
OS	FER1L4	Tumor Suppressor	30 pairs of OS and ANCTs	hFOB1.19, MG63, U2OS, HOS, Saos-2	miR-18a-5p, SOCS5	EMT	FER1L4 by targeting miR-18a-5p/ SOCS5 could induce apoptosis and suppress EMT via activating PI3K/ Akt pathway in OS.	(129)
OS	LINC00628	Tumor Suppressor	80 pairs of OS and ANCTs	NHOst, HOS, MG-63, SOSP-9607, U2OS	_	_	LINC00628 could inhibit proliferation, invasion, and migration and also promote apoptosis in OS cells through inactivating PI3K/Akt signaling pathway.	(130)
Gastric Cancer (GC)	PICART1	Tumor Suppressor	Mouse/ human; 40 pairs of GC and ANCTs	HGC27, GES-1, BGC823, SGC7901, MGC803	_	MAPK/ERK	PICART1 could inhibit cell proliferation and inhibit apoptosis via PI3K/Akt and MAPK/ERK signaling pathways in GC.	(131)
GC	LOC101928316	Tumor Suppressor	Mouse/ human; 90 pairs of GC and ANCTs	MKN-28, GES-1, BGC-823, SGC-7901, MGC-803, MKN-45,	_	mTOR	LOC101928316 could attenuate proliferation, migration, and invasion in GC cells via PI3K/Akt/ mTOR pathway.	(132)
GC	ADAMTS9-AS2	Tumor Suppressor	71 pairs of GC and ANCTs	GES-1, MKN74, SGC-7901, NUGC-4, HGC-27	_	_	ADAMTS9-AS2 could inhibit GC cell proliferation, migration and invasion, and induce apoptosis.	(125)
GC	SLC25A5-AS1	Tumor Suppressor	Mouse/ human; 56 pairs of GC and ANCTs	GES-1, AGS, SGC-7901, BGC-823, HGC-27	miR-19a-3p, PTEN	_	SLC25A5-AS1 by targeting miR-19a-3p could inhibit cell proliferation, cell cycle progression, and promote apoptosis via PTEN/PI3K/AKT axis in GC.	(133)
Glioma	MEG3	Tumor Suppressor	Mouse/ human; 30 pairs of glioma and ANCTs	U-251, M059J	miR-93	_	MEG3 by targeting miR-93 could inhibit cell growth and induce apoptosis in glioma cells via the PI3K/Akt pathway.	(134)
Colorectal Cancer (CRC)	AB073614	Tumor Suppressor	28 pairs of CRC and ANCTs	SW480	_	_	AB073614could prevent proliferation and metastasis of CRC cells.	(135)
CRC	ST3Gal6-AS1	Tumor Suppressor	Mouse/ human; 45 pairs of CRC and ANCTs	SW480, SW620, LOVO, U937, HL60, SW1353, HeLa, 293 T, ACHN, HepG2, MCF-7	_	_	ST3Gal6-AS1 could inhibit CRC cell proliferation, metastasis, and promote apoptosis by modulating α-2,3 sialylation.	(136)
CRC	SNHG6	Tumor Suppressor	30 pairs of CRC and ANCTs	SW480, HCT-116, NCM460	ETS1	mTOR	SNHG6 by targeting ETS1 could inhibit cell proliferation and metastasis via PI3K/Akt/mTOR signaling pathways.	(137)
CRC	LINC02381	Tumor Suppressor	20 pairs of CRC and ANCTs/ TCGA dataset	U87, A172, LNCaP, 1321, SKNMC, MCF7, SK-BR-3, 5637	PTEN	_	LINC02381 by regulating PTEN could inhibit cell proliferation and enhance apoptosis in CRC via the PI3K/Akt pathway.	(138)
Bladder Cancer (BCa)	LINC00641	Tumor Suppressor	Mouse/ human; 39 pairs of BCa and ANCTs	T24, SW780, J82, SV-HUC-1	miR-197-3p, KLF10, PTEN	_	LINC00641by targeting miR-197-3p/KLF10 could attenuate proliferation, migration, and invasion in BCa via PTEN/PI3K/ Akt cascade.	(139)
Hepatocellular Carcinoma (HCC)	TCL6	Tumor Suppressor	GEO database	HepG2, 293 T, SMCC-7721, MHCC-97H, HUH7, LO2	miR-106a-5p, PTEN	_	TCL6 by targeting miR-106a-5p could attenuate proliferation, migration, and invasion in HCC via PTEN/PI3K/Akt axis.	(126)
HCC	FER1L4	Tumor Suppressor	31 pairs of HCC and ANCTs	HepG-2, Hep3b, SMMC-7721, HL-7702	_	_	FER1L4 could suppress proliferation and migration in HCC via regulating the PI3K/AKT signaling pathway.	(140)
Retinoblastoma (RB)	CANT1	Tumor Suppressor	Mouse, GEO database	293 T, Y79, Weri-Rb1, RB44	PI3Kγ	_	CANT1 by directly binding to the PI3Kγ promoter could suppress tumor progression in RB via the PI3K/Akt pathway.	(141)
Lung Cancer	FER1L4	Tumor Suppressor			_	_		(142)

(*continued on next page*)

Table 4 (*continued*)

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Assessed Cell line	Targets/ Regulators	Additional pathway	Function	Refs.
			100 pairs of lung cancer and ANCTs	BEAS-2B, 95D, SPC-A-1, A549, H1975, H-125			FER1L4 could inhibit cell proliferation and metastasis in lung cancer cells.	
Lung Cancer	FOXO1	Tumor Suppressor	Mouse/ human; 20 pairs of lung cancer and ANCTs	A549, H460, HCC827, H1299, IMR-90	Myc, Cyclin D1	_	FOXO1 could inhibit lung cancer cell growth by downregulating the PI3K/Akt signaling pathway.	(143)
Breast Cancer (BC)	MEG3	Tumor Suppressor	Mouse/ human; 20 pairs of BC and ANCTs	MCF-7, MDA-MB-231, MDA-MB-453, T47D, MCF-10A	miR-21	Glycolysis	MEG3 by targeting miR-21 could inhibit tumorigenesis and glycolysis in BC cells via the PI3K/ Akt pathway.	(144)
Renal Cancer (RC)	LINC00982	Tumor Suppressor	96 pairs of RC and ANCTs	HK-2, 786-O, 769-P, ACHN, A-498	_	_	LINC00982 could inhibit cell proliferation and promote apoptosis through PI3K/Akt signaling pathway in renal cancer.	(127)
Multiple Myeloma (MM)	OIP5-AS1	Tumor Suppressor	Mouse/ human; 97 MM tissues and 14 healthy control	NCI-H929, U266, RPMI-8266, nPC	miR-410, KLF10, PTEN	_	OIP5-AS1 by suppressing miR-410/ KLF10 could inhibit cell proliferation and apoptosis in MM.	(145)

expression of this lncRNA was an independent prognostic factor in AML patients with the normal karyotype. In vitro investigations demonstrated that knock-down of this lncRNA resulted in inhibition of growth of leukemic cells through stimulation of cell cycle arrest and apoptosis. Moreover, HOXA-AS2 silencing decreased phosphorylation of PI3K and AKT therefore enhanced expression of P21 and P27. SOX4 has been suggested as one of the main targets of this lncRNA in AML [147]. Wei et al. have reported over-expression of BCAR4 in glioma tissues compared with paired non-tumor samples. Up-regulation of this lncRNA was correlated with short overall survival of these patients. BCAR4 silencing suppressed cell proliferation, while its up-regulation enhanced proliferation of glioma cells. Mechanistically, BCAR4 induces PI3K/AKT signaling via enhancing the expression of EGFR. Taken together, BCAR4 enhances progression of glioma through promoting activity of EGFR/-PI3K/AKT axis [148]. Han et al. have assessed the expression profile of CASC11 in HCC samples from the Cancer Genome Atlas (TCGA) database. They reported an association between over-expression of CASC11 poor overall survival rate of HCC patients. Subsequently, they confirmed these results in another set of HCC patients. CASC11 silencing inhibited cell migration, invasion, and EMT. Expression of this lncRNA was induced by the transcription factor STAT3. CASC11 was shown to decrease expression of PTEN through binding with EZH2 [149]. Fig. 3 represents dysregulation of a number of lncRNAs which have a remarkable oncogenic role via reguklating PI3K/AKT signaling cascade.

9. Biomarker role of PI3K/AKT-associated lncRNAs

PI3K/AKT-associated lncRNAs have been shown to have the potential to be used as diagnostic/ prognostic markers. For instance, SLC25A5-AS1, TINCR, MALAT1, and have diagnostic power values of 0.76, 0.92, and 0.95 in gastric, colorectal, and squamous cell carcinoma patients, respectively [203,208,214]. Moreover, LINC00265 had a diagnostic value of 0.81 in AML patients [164]. Over-expression of several lncRNAs such as HOXA-AS2, HAGLROS, HOTTIP, and MALAT1 has been recognized as markers for poor survival of cancer patients [147,153,199,202]. Table 6 summarizes the results of studies that evaluated the diagnostic or prognostic potential of PI3K/AKT-associated lncRNAs in human malignancies.

10. Discussion

PI3K/AKT signaling participates in the phosphorylation of numerous molecules that control cell growth, proliferation, metabolism, and survival. This pathway is commonly activated in human malignancies [2]. Accordingly, several inhibitors have been designed to target kinases in this pathway and their efficacy is being assessed in clinical trials. Yet, their effectiveness can be restricted by some mechanisms such as FOXO- and mTORC1-associated feedback loops that reactivate this pathway [2]. NcRNAs contribute to the regulation of several proteins in the PI3K/AKT pathway including proteins that mediate these feedback loops [112], thus identification of the exact function of ncRNAs would facilitate the design of targeted therapies against this pathway with higher efficiencies in the treatment of cancer patients.

The effects of ncRNAs in the regulation of the PI3K/AKT pathway has been vastly assessed in solid tumors. However, this research avenue has been less explored in leukemia/ lymphoma. Based on the importance of inhibitors of this pathway in the treatment of patients with leukemia or lymphoma [215,216], identification of the role of ncRNAs in the regulation of the PI3K/AKT pathway in these malignancies would facilitate recognition of the mechanisms of resistance to these kinds of treatments in these patients. A number of these ncRNAs influence activity of other cancer-related pathways such as Wnt/β-catenin, mTOR, and NF-κB pathways, thus providing a functional link between these signaling pathways. Besides, the EMT process is an essential cellular process that is influenced by these ncRNAs. Thus, therapeutic intervention with the expression of these ncRNAs is expected to affect the invasive properties of cancer cells.

Notably, activation of the PI3K/AKT/mTOR pathway influences the response of cancer cells to chemotherapeutic agents and endocrine therapies through modulation of autophagy [217,218]. Therefore, ncRNAs that modulate the activity of this pathway have practical significance in the determination of the response of patients to a wide range of therapeutic modalities. These transcripts also modulate the EMT process and cancer stem cell phenotype through regulation of expression of PTEN and several EMT-associated genes [219,220], thus influencing metastatic potential, invasiveness, and cancer recurrence. Moreover, PI3K/AKT-associated ncRNAs can predict the clinical ouutcome of patienst with diverse neoplastic conditions, emphasizing their prominnet roles in the pathogenesis of neoplasms. Both lncRNAs and miRNAs can be detected in the peripheral blood, urine samples or other body

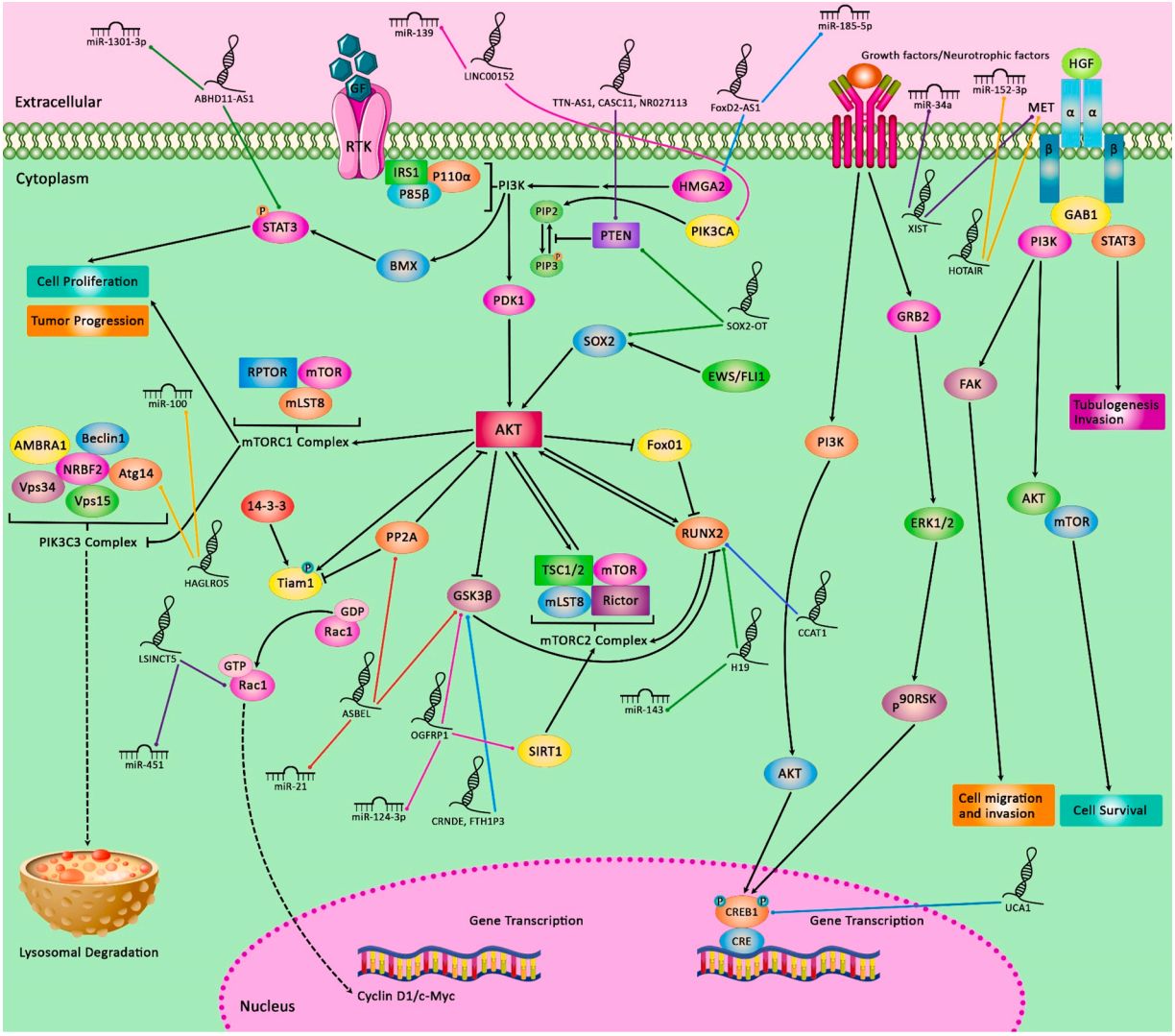

Fig. 3. A schematic summary of lncRNAs triggering various human cancers via the PI3K/AKT signaling pathway. Over-expression of various lncRNAs could play an important role in cancers via changing activity of PI3K/AKT cascade. Aberrant expression of different lncRNAs like CCAT1, OGFRP1, TTN-AS1, HAGLROS, FoxD2-AS1, and ASBEL could result in tumorigenesis of cervical cancer, endometrial cancer, lung adenocarcinoma, nasopharyngeal carcinoma, glioma, and osteosarcoma through directly targeting Runx2, miR-124-3p, SIRT1, PTEN, miR-100, ATG14, miR-185-5p, HMGA2, miR-21, PP2A, and GSK3β via PI3K/AKT signaling pathway. Therefore, suppressing the expression level of these oncogenes may be regarded as a helpful approach for the management of these cancers [150–157]. Table 5 shows the function of oncogenic lncRNAs in the regulation of the PI3K/AKT pathway in cancer.

Table 5
The function of oncogenic lncRNAs in the regulation of PI3K/AKT pathway in cancer (ANCTs: adjacent non-cancerous tissues).

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
Cervical Cancer (CC)	RP1-93H18.6	Oncogene	Mouse/human; 78 pairs of CC and ANCTs/ GEO database	END1/E6E7, SiHa, HeLa, Caski, 293 T, C-33A	_	_	RP1-93H18.6 could enhance proliferation, migration, and invasion and also induce metastasis.	[146]
CC	CCAT1	Oncogene	Mouse/human; 23 pairs of CC and ANCTs	HeLa, SiHa	Runx2	EMT	CCAT1 by targeting Runx2 could inhibit proliferation and EMT of CC cells via the PI3K/ Akt pathway.	[158]
CC	LINC01305	Oncogene	_	SiHa, Hela, C-33A, Caski, ME-180, MS751	TNXB	EMT	LINC01305 by targeting TNBX could enhance EMT, invasion, and migration in CC.	[159]
CC	MFI2	Oncogene	Mouse/human; 35 pairs of CC and ANCTs	SiHa, Caski, C33A, HeLa, NCEC	_	_	MFI2 could promote cell proliferation, metastasis, and inhibit apoptosis in CC via the PI3K/Akt signaling pathway.	[160]
CC	ANRIL	Oncogene	53 pairs of CC and ANCTs	HeLa, CaSki, SiHa, ME-180, H8	_	_	ANRIL could enhance proliferation, migration, and invasion in CC.	[161]
Ovarian Cancer (OC)	MALAT1	Oncogene	Mouse/human; 64 EOC tissues and 30 normal control	SKOV3, OVCAR3, HO8910, A2780, HO8910PM	_	EMT	MALAT1 could promote proliferation, metastasis, and EMT in EOC.	[162]
Endometrial Cancer	OGFRP1	Oncogene	48 pairs of endometrial cancer and ANCTs	HHUA, KLE, Ishikawa, ECC-1, NE	miR-124-3p, SIRT1, GSK-3β	_	OGFRP1 by targeting miR-124-3p/SIRT1 could enhance migration, invasion, and inhibit apoptosis via activating PI3K/ Akt/GSK-3β axis.	[151]
Endometrial Cancer	LINP1	Oncogene	Mouse/human; 35 pairs of endometrial cancer and ANCTs	KLE, AN3CA, ECC-1, T-HESC	_	_	LINP1 could increase cell proliferation and metastasis in endometrial cancer.	[163]
Acute Myeloid Leukemia (AML)	HOXA-AS2	Oncogene	108 Bone marrow (BM) tissues and 6 normal control	HL-60, U937, THP-1, OCI-AML3, NB4, Kasumi-1, K562, 293 T	SOX4	P21, P27	HOXA-AS2 by targeting SOX4 could promote the proliferation of leukemic cells and repress cell apoptosis via the PI3K/Akt signaling pathway.	[147]
AML	LINC00265	Oncogene	135 BM and PBS of AML patients	HL-60, NB4, HS-5	_	_	LINC00265 could promote AML cell proliferation, migration, invasion, and suppress apoptosis via the PI3K-Akt pathway.	[164]
Chronic Myeloid Leukemia (CML)	HULC	Oncogene	35 BM of CML patients	K562, KG-1, THP-1	miR-200a, c-Myc	_	HULC by targeting miR-200a/ c-Myc could promote cell proliferation and oncogenesis in CML.	[165]
Lung Cancer	OECC	Oncogene	50 pairs of lung cancer and ANCTs	BEAS-2B, H1975, A549, SPC-A-1, 95D, H-125	_	mTOR	OECC could promote cell proliferation and metastasis via the PI3K/Akt/mTOR signaling pathway in lung cancer.	[166]
Lung Cancer	HOXB-AS3	Oncogene	Mouse/human; 30 pairs of lung cancer and ANCTs	H1795, H460, SPC-A1, A549, 16HBE	_	_	HOXB-AS3 regulates proliferation, metastasis, and invasion via modulating the PI3K/Akt pathway.	[167]
Lung Adenocarcinoma (LAD)	TTN-AS1	Oncogene	_	BEAS-2B, H157, HCC827, H1975, H1299, A549	PTEN	_	TTN-AS1 by destabilizing PTEN could promote progression of LAD via PI3K/Akt signaling pathway	[152]
HCC	CASC11	Oncogene	76 pairs of HCC and ANCTs	HepG2, Hep3B, SMMC-7721, LM3, LO2	PTEN	EMT	STAT3-induced CASC11 by targeting PTEN could promote cell migration, invasion, and EMT in HCC via activating PI3K/Akt signaling pathway.	[149]
HCC	LINC00152	Oncogene	Mouse/human; 70 pairs of HCC and ANCTs	Hep3B, HCCLM3, MCC97H, HepG2, L02	miR-139, PIK3CA	mTOR	LINC00152 by targeting miR-139/PIK3CA could promote proliferation, migration, and invasion and also inhibit apoptosis in HCC.	[168]
HCC	MALAT1	Oncogene	40 HCC tissues and 12 normal control	LO2, HepG2, Huh7	miR-146a	mTOR, autophagy	MALAT1 by targeting miR-146a could inhibit apoptosis and autophagy of HCC cells via PI3K/Akt/mTOR signaling pathway.	[169]
HCC	LINC01133	Oncogene	Mouse	HepG2, Hep3B, MHCC-97 L, SK-	_	_	LINC01133 could enhance proliferation, migration, and	[170]

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Table 5 (*continued*)

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
				Hep-1, MHCC-97H, HL-7702			invasion, and also inhibit apoptosis in HCC via PI3K/Akt.	
HCC	NR027113	Oncogene	134 pairs of HCC and ANCTs	Bel-7402, SK-HEP-1, PLC/ PRF/5, MHCC97H, SMMC-7721, LO2	PTEN	EMT	NR027113 by targeting could enhance proliferation, migration, and invasion in HCC via EMT process and PI3K/Akt pathway.	[171]
HCC	CDKN2B-AS1	Oncogene	Mouse/human; 100 pairs of HCC and ANCTs	LO2, HepG2, Huh7, SMMC-7721	let-7c-5p, NAP1L1	mTOR	CDKN2B-AS1 by targeting let-7c-5p/NAP1L1 could promote tumor growth and metastasis in HCC via PI3K/Akt/mTOR signaling pathway.	[172]
HCC	PTTG3P	Oncogene	Mouse/136; HCC and ANCTs	HepG2, Hep3B	PTTG1	EMT	PTTG3P by targeting PTTG1 could promote cell growth, metastasis and inhibit apoptosis via PI3K/Akt signaling in HCC.	[173]
HCC	CRNDE	Oncogene	Mouse/human; 23 pairs of HCC and ANCTs	QSG-7701, Hep3B, Huh7	GSK3β	Wnt/ β-catenin	CRNDE could promote HCC cell proliferation by regulating the PI3K/Akt/GSK3β-Wnt/ β-catenin signaling pathway.	[174]
Pancreatic Ductal Adenocarcinoma (PDAC)	SNHG1	Oncogene	Mouse/human; 46 pairs of PDAC and ANCTs	Panc-1, BxPC-3, SW1990, HPDE6	_	_	SNHG1 enhances PDAC tumorigenesis by inducing PI3K/AKT signaling pathway.	[175]
Pancreatic Cancer (PC)	HULC	Oncogene	26 pairs of PC and ANCTs	Panc-1	miR-15a	_	HULC by targeting miR-15a could promote proliferation, migration, and invasion of pancreatic cancer cells via the PI3K/Akt pathway.	[176]
PC	ABHD11-AS1	Oncogene	147 pairs of PC and ANCTs	Capan-2, L3.6 pl, BxPC3, AsPC-1, PANC-1, HPDE6-C7	_	EMT	ABHD11-AS1 could promote proliferation, migration, invasion, and EMT in PC via PI3K/Akt signaling pathway.	[177]
Cholangiocarcinoma (CCA)	SOX2-OT	Oncogene	Mouse/human; 82 pairs of CCA and ANCTs	HuH-28, QBC939, HuCCT1, CCLP1, RBE, HIBEC	SOX2, PTEN	_	IRF4-induced SOX2-OT by targeting SOX2 could promote the progression of CCA via activating the PI3K/Akt signaling pathway.	[178]
Thyroid Cancer (TC)	H19	Oncogene	30 pairs of TC and ANCTs	FTC-133, TPC-1	_	_	H19 could enhance cell viability and inhibit apoptosis of TC cells	[179]
TC	XIST	Oncogene	Mouse/human; 77 pairs of TC and ANCTs	FTC133, BCPAP, TEC, TPC-1, SW1736, KAT18	miR-34a	MET	XIST by targeting miR-34a could enhance cell proliferation and tumor growth in thyroid cancer via MET/PI3K/Akt signaling pathway.	[180]
Papillary Thyroid Carcinoma (PTC)	ABHD11-AS1	Oncogene	Mouse/human; 82 pairs of PTC and ANCTs	BCPAP, Nthy-ori 3-1, K1, BHP5-16, BHP2-7	miR-1301-3p, STAT3	_	STAT3-induced ABHD11-AS1 by targeting miR-1301-3p/ STAT3 could promote tumor progression in PTC via PI3K/ Akt signaling pathway.	[181]
Prostate Cancer (PCa)	ZEB1-AS1	Oncogene	30 pairs of PCa and ANCTs/ starBase database	RWPE-1, DU145, LNCaP	miR-342-3p, CUL4B	mTOR	ZEB1-AS1 by regulating miR-342-3p/CUL4B could increase proliferation, migration, and invasion in PCa via PI3K/Akt/ mTOR pathway.	[182]
Non-Small Cell Lung Carcinoma (NSCLC)	NORAD	Oncogene	Mouse/human; 26 pairs of NSCLC and ANCTs	NHBE, 293 T, A549, H1299, H460, Calu3, SK-MES-1	miR-520a-3p	mTOR	NORAD by targeting miR-520a-3p could enhance proliferation, migration, and invasion.	[183]
NSCLC	CRNDE	Oncogene	Mouse/human; 30 pairs of NSCLC and normal control tissues	A549, PC-9, SK-MES-1, 16HBE	_	_	CRNDE could promote cell proliferation through PI3K/Akt signaling in NSCLC.	[184]
Nasopharyngeal Carcinoma (NPC)	HAGLROS	Oncogene	88 pairs of NPC and ANCTs	SUNE1, 6-10B, HK1, 5–8F	miR-100, ATG14	mTOR, autophagy	HAGLROS by targeting miR-100/ATG14 could confer cell viability, autophagy and enhance apoptosis via PI3K/ Akt/mTOR.	[153]
Glioma	BCAR4	Oncogene	92 pairs of glioma and ANCTs	U87, U251, LN229, T98 G, NHAs	EGFR	_	BCAR4 could promote glioma cell proliferation and inhibit apoptosis via EGFR/PI3K/AKT cascade.	[148]
Glioma	LSINCT5	Oncogene	56 G tissues, 16 healthy normal control	GL15	miR-451, Rac1		LSINCT5 by targeting miR-451 could confer glioma cells	[185]

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Table 5 (*continued*)

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
						Wnt/b-catenin, NF-κB	growth and metastasis via inhibiting Rac1-regulated PI3K/AKT, Wnt/b-catenin, and NF-κB pathways.	
Glioma	FoxD2-AS1	Oncogene	Mouse/human; 48 G tissues, and 24 healthy normal control/ GEO database	U87, A172, U251, T98 G, HEB	miR-185-5p, HMGA2	_	FoxD2-AS1by targeting miR-185-5p/HMGA2 could promote tumor progression and metastatic potential of glioma cells.	[154]
Glioma	SNHG20	Oncogene	80 pairs of G and ANCTs	U118, U251	_	_	SNHG20 by targeting PTEN could decrease apoptosis and induce cell proliferation in glioma via PI3K/Akt signaling pathway.	[186]
Glioma	LINC01426	Oncogene	86 pairs of G and ANCTs/ TCGA database	PG1, A172, LN229, U251, LN118, H4	_	_	LINC01426 could confer glioma cells proliferation, migration, and invasion, and induce apoptosis.	[187]
Osteosarcoma (OS)	UCA1	Oncogene	Mouse/human; 30 pairs of OS and ANCTs	hFOB1.19, Saos-2, HOS, U2-OS, MG-63	CREB1	EMT, mTOR	UCA1 by targeting CREB1 could promote OS invasion and metastasis through EMT and activating PI3K/Akt/mTOR pathway.	[188]
OS	DBH-AS1	Oncogene	119 pairs of OS and ANCTs	U2OS, Saos-2, HOS, MG63, hFOB1.19	_	_	DBH-AS1 could inhibit cell proliferation, migration, and invasion, and also promote apoptosis in OS.	[189]
OS	ANRIL	Oncogene	Mouse/human; 57 pairs of OS and ANCTs	MNNG/HOS, U2OS	_	_	ANRIL could promote tumorigenesis in OS cells via the PI3K/Akt signaling pathway.	[190]
OS	ASBEL	Oncogene	_	hFOB1.19, MG63, OS-732	miR-21, PP2A, GSK3β	MEK/ERK	ASBEL by targeting miR-21/ PP2A could promote proliferation, migration, and invasion in OS via regulating PI3K/AKT/GSK3β and MEK/ ERK signaling pathways.	[155]
OS	LINC00968	Oncogene	Mouse	U2OS, MG63, Saos-2, 143-B, SW1353, hFOB	_	mTOR	LINC00968 could increase cell proliferation, migration, and invasion.	[191]
OS	MALAT1	Oncogene	Mouse/human; 68 pairs of OS and ANCTs	MG63, U2OS, Saos-2, 293 T, SOSP-9607, SW1353, hFOB1.19, NIH3T3	miR-129-5p, RET	_	MALAT1 by targeting miR-129-5p/RET could promote proliferation and migration in OS via the PI3K/Akt pathway.	[192]
Melanoma	MIAT	Oncogene	20 pairs of melanoma and ANCTs	HaCaT, A-375, SK-MEL-28, M21, A2508	_	_	MIAT could promote melanoma migration and invasion.	[193]
Melanoma	OR3A4	Oncogene	50 melanoma tissues and 33 skin tissues with melanocytic nevus	SK-MEL-28, WM266-4, A375, SK-MEL-2	_	_	OR3A4 could promote invasion and migration in melanoma by inducing PI3K/Akt cascade.	[194]
Melanoma	MHENCR	Oncogene	Mouse/human; 30 pairs of melanoma and ANCTs	A375, SK-MEL-2	miR-425/-489	_	MHENCR by targeting miR-425/-489 could enhance proliferation, induce cell cycle arrest and apoptosis, and also reduce melanoma growth and metastasis.	[195]
Melanoma	HOTAIR	Oncogene	Mouse/human; 60 pairs of melanoma and ANCTs	A375, A875, SK-MEL-1, SK-MEL-5, SK-MEL-28	miR-152-3p, c-MET	mTOR	HOTAIR by targeting miR-152-3p/c-MET could enhance tumor growth and metastasis via PI3K/Akt/mTOR pathway.	[196]
Melanoma	H19	Oncogene	49 pairs of melanoma and ANCTs	C32, SK-MEL-28, CCD-1059Sk	_	NF-κB	H19 could inhibit migration and invasion of melanoma cells by inactivating NF-κB and PI3K/Akt cascades.	[197]
Clear Cell Renal Cell Carcinoma (ccRCC)	TP73-AS1	Oncogene	40 pairs of ccRCC and ANCTs	A498, Caki1, Caki2	KISS1	mTOR	TP73-AS1 by repressing KISS1 could promote cell proliferation and inhibit apoptosis via inactivating PI3K/Akt/mTOR signaling pathway.	[198]
Renal Cell Carcinoma (RCC)	HOTTIP	Oncogene	Mouse/human; 42 pairs of RCC and ANCTs	786-O, A498, ACHN, OSRC-2	Atg13	autophagy	HOTTIP by regulating autophagy could increase RCC	[199]

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Table 5 (*continued*)

Cancer type	lncRNA	Role of lncRNA	Human/ Animal	Cell line	Targets/ Regulators	Additional pathway	Effect	Refs.
							progression via the PI3K/Akt/ Atg13 axis.	
RCC	MALAT1	Oncogene	30 pairs of RCC tissues and ANCTs	786-O, Caki-1, Ketr-3, RT112, T24, Ect1/E6E7	miR-22-3p	_	MALAT1 by targeting miR-22-3p could enhance proliferation, migration, and mobility in RCC.	[200]
Retinoblastoma (RB)	H19	Oncogene	_	Y79	miR-143, RUNX2	mTOR	H19 by targeting miR-143/ RUNX2 could enhance proliferation, migration, invasion, and inhibit apoptosis via PI3K/Akt/mTOR.	[201]
Gastric Cancer (GC)	MALAT1	Oncogene	64 pairs of GC and ANCTs, and 64 healthy normal control	SNU-1, AGS	_	_	MALAT1 could promote proliferation, migration, and invasion of GC.	[202]
Colorectal Cancer (CRC)	TINCR	Oncogene	Mouse/human; 80 pairs of CRC and ANCTs	FHC, HCT116, HCT8, HT29, SW620, SW480	miR-7-5p	mTOR	TINCR by targeting miR-7-5p could enhance proliferation, migration, invasion, and induce metastasis in CRC via PI3K/ Akt/mTOR signaling pathway.	[203]
CRC	DLX6-AS1	Oncogene	Mouse/human; 60 pairs of CRC and ANCTs	NCM460, HCT116, HT-29, SW480	_	mTOR	DLX6-AS1 could promote cell proliferation, invasion, and migration via modulating PI3K/Akt/mTOR pathway.	[204]
CRC	SNHG7	Oncogene	123 pairs of CRC and ANCTs	caco2, SW480, SW620, FHC, Hct116, LoVo	miR-34a, GALNT7	mTOR	SNHG7 by targeting miR-34a/ GALNT7 could enhance proliferation, migration, and invasion in CRC via PI3K/Akt/ mTOR pathway.	[205]
CRC	LINC01296	Oncogene	Mouse/human; 36 pairs of CRC and ANCTs	SW620, LoVo, SW480, HCT-8, HCT-8/5-FU	miR-26a, GALNT3, MUC1	_	LINC01296 by targeting miR-26a/GALNT3 could develop CRC progression by regulating O-glycosylated MUC1.	[206]
CRC	PlncRNA-1	Oncogene	Mouse/human; 77 pairs of CRC and ANCTs	SW480, DLD-1, HCT116, SW620, HcoEpiC	_	_	PlncRNA-1 could promote CRC cell progression, invasion, and migration viaPI3K/Akt Signaling Pathway.	[207]
Tongue Squamous Cell Carcinoma (TSCC)	MALAT1	Oncogene	72 pairs of OSCC and ANCTs	SCC4, SCC15, SCC25, Hs 680. Tg	MMP-9	_	MALAT1 by regulating MMP-9 could confer tumor growth in TSCC via PI3K/Akt signaling pathway.	[208]
Oral Squamous Cell Carcinoma (OSCC)	FTH1P3	Oncogene	134 pairs of OSCC and ANCTs	SNU1041, SCC25, SCC4, SCC9, hNOK	GSK3b	Wnt/ β-catenin	FTH1P3 could promote OSCC cells migration and invasion by promoting PI3K/Akt/GSK3b/ Wnt/β-catenin signaling.	[209]
Salivary Adenoid Cystic Carcinoma (SACC)	ADAMTS9-AS2	Oncogene	Mouse/human; 102 pairs of SACC and ANCTs	SACC-83, SACC-LM	miR-143-3p, ITGA6	MEK/ERK	ADAMTS9-AS2 by targeting miR-143-3p/ITGA6 could promote proliferation, migration, invasion, and metastasis in SACC.	[210]
Medulloblastoma	LOXL1-AS1	Oncogene	Mouse/human; 50 pairs of Medulloblastoma and ANCTs	Daoy, D283, D425, D341, D458	_	EMT	LOXL1-AS1 could promote proliferation, metastasis, and EMT in medulloblastoma via activating PI3K/Akt pathway.	[211]
Esophageal Squamous Cell Carcinoma (ESCC)	CASC9	Oncogene	Mouse/human; 115 ESCC and ANCTs	Het-1A, EC109, KYSE150, KYSE450	LAMC2	FAK	CASC9 by targeting LAMC2 could promote migration, invasion, and metastasis in ESCC via FAK/PI3K/Akt signaling pathway.	[212]
Bladder Cancer (BCa)	HULC	Oncogene	Mouse/human; 276 pairs of BCa and ANCTs	T24, RT4	ZIC2	_	HULC by targeting ZIC2 could promote BCa cell proliferation and inhibit apoptosis.	[213]

fluids, representing their position in non-invasive diagnosis of neoplastic conditions.

LncRNAs regulate the activity of the PI3K/AKT pathway through different mechanisms among them is acting as competing endogenous RNAs for miRNAs. Several pairs of lncRNA/ miRNA have been recognized that modulates the function of this pathway in different types of cancers, for instance, lncRNA 691/miR-9-5p and GAS5/miR-23a-3p in osteosarcoma [124,128], MEG3/miR-21 in breast cancer [144] and TCL6/miR-106a-5p in HCC [126]. Thus, the functional interaction between these two kinds of ncRNAs is a well-recognized mechanism for induction or suppression of this pathway. Any putative targeted therapy against the PI3K/AKT pathway should consider the complex interactions between miRNAs and lncRNAs. The miRNA/lncRNA/mRNA trios in the context of PI3K/AKT signaling can be used as therapeutic targets for efficiently modulating activity of this molecular axis.

PIK3/AKT-associated ncRNAs have the potential to be applied as diagnostic/ prognostic biomarkers in cancer patients. Based on the functional link between these transcripts, it is expected that a combination of expression levels of a number of these ncRNAs would facilitate the design of diagnostic/prognostic panels with high accuracies.

Table 6
Diagnostic/ prognostic role of PI3K/AKT-associated lncRNAs in human cancers.

Samples	Area Under Curve	Sensitivity	Specificity	Kaplan-Meier Analysis	Univariate Cox Regression	Multivariate Cox Regression	Ref
108 AML patients	_	_	_	High amounts of HOXA-AS2 were associated with shorter OS and RFS.	_	High expression of HOXA-AS2 was correlated with MRD positivity.	[147]
88 NPC patients	_	_	_	High amounts of HAGLROS were associated with shorter OS rate.	_	_	[153]
92 glioma patients	_	_	_	High amounts of BCAR4 were associated with shorter OS rate.	_	High expression of BCAR4 was correlated with advanced WHO grade.	[148]
42 RCC patients	_	_	_	Up-regulation of HOTTIP was associated with a shorter OS rate.	-	_	[199]
64 GC patients	_	_	_	High expression of MALAT1 was associated with a shorter OS rate.	_	_	[202]
56 GC patients	0.7699 (SLC25A5-AS1)	_	_	_	_	_	[133]
76 HCC patients	_	_	_	Up-regulation of CASC11 was associated with a shorter OS rate.	_	_	[149]
82 PTC patients	_	_	_	Up-regulation of ABHD11-AS1 was associated with a shorter OS rate.	_	_	[181]
80 CRC patients	0.922	97.5	80.0	Up-regulation of TINCR was associated with a shorter OS rate.	_	High expression of TINCR was correlated with tumor differentiation and TNM stage.	[203]
119 OS patients	_	_	_	Up-regulation of DBH-AS1 was associated with a shorter OS rate.	_	High expression of DBH-AS1 was correlated with advanced lymph node status and metastasis status.	[189]
72 TSCC patients	0.9514	_	_	High expression of MALAT1 was associated with a shorter OS rate.	_	_	[208]
57 OS patients	_	_	_	High expression of ANRIL was associated with a shorter OS rate.	_	_	[190]
102 SACC patients	_	_	_	High expression of ADAMTS9-AS2 was associated with a shorter OS rate.	_	_	[210]
23 HCC patients	_	_	_	Up-regulation of CRNDE was associated with shorter OS and DFS rates.	_	_	[174]
36 CRC patients	_	_	_	Up-regulation of LINC01296 was associated with a shorter OS rate.	_	_	[206]
40 ccRCC patients	_	_	_	High expression of TP73-AS1 was associated with shorter OS and DFS rates.	_	_	[198]
77 TC patients	0.7360	_	_	High expression of XIST was associated with a shorter OS rate.	High expression of XIST was correlated with TNM stage.	_	[180]
115 ESCC patients	_	_	_	High expression of CASC9 was associated with a shorter OS rate.	_	_	[212]
39 BCa patients	_	_	_	Low expression of LINC00641was associated with shorter OS and PFS rates.	_	_	[139]
53 CRC patients	_	_	_	High expression of SNHG7 was associated with shorter OS and DFS rates.	_	High expression of SNHG7 was correlated with lymphatic metastasis, distant metastasis, and tumor stage.	[205]
100 HCC patients, TCGA database	_	_	_	High expression of CDKN2B-AS1 was associated with a shorter OS rate.	_	_	[172]
136 HCC patients	_	_	_	High expression of PTTG3P was associated with a shorter OS rate.	High expression of PTTG3P was correlated with tumor size.	High expression of PTTG3P was correlated with advanced TNM stage.	[173]
68 OS patients	_	_	_	High expression of MALAT1 was associated with shorter OS and DFS rates.	_	High expression of MALAT1 was correlated with tumor size and metastasis.	[192]
71 GC patients	_	_	_	Low expression of ADAMTS9-AS2 was associated with a shorter OS rate.	_	_	[125]
77 CRC patients	_	_	_		_	_	[207]

(*continued on next page*)

Table 6 (*continued*)

Samples	Area Under Curve	Sensitivity	Specificity	Kaplan-Meier Analysis	Univariate Cox Regression	Multivariate Cox Regression	Ref
				High expression of PlncRNA-1 was associated with a shorter OS rate.			
147 PC patients	_	_	_	High expression of ABHD11-AS1 was associated with shorter OS and DFS rates.	_	High expression of ABHD11-AS1 was correlated with distant metastasis, TNM stage, and tumor differentiation.	[177]
134 OSCC patients	_	_	_	High expression of FTH1P3 was associated with a shorter OS rate.	_	High expression of FTH1P3 was correlated with T classification, N classification, and TNM stage.	[209]
82 CCA patients	_	_	_	High expression of SOX2-OT was associated with a shorter OS rate.	_	_	[178]
135 AML patients	0.8131	72.43	91.45	High expression of LINC00265 was associated with a shorter OS rate.	_	High expression of LINC00265 was correlated with FAB classification and cytogenetics.	[164]
134 HCC patients	_	_	_	High expression of NR027113 was associated with shorter OS and DFS rates.	_	_	[171]
glioma patients, TCGA database	_	_	_	High expression of LINC01426 was associated with shorter OS and DFS rates.	_	High expression of LINC01426 was negatively correlated with WHO grade and KPS score.	[187]
80 OS patients	_	_	_	Low expression of LINC00628 was associated with a shorter OS rate.	_	_	[130]
53 CC patients	_	_	_	High expression of ANRIL was associated with a shorter OS rate.	_	High expression of ANRIL was correlated with FIGO stage and lymph node metastasis.	[161]
276 BCa patients	_	_	_	High expression of HULC was associated with a shorter RFS rate.	_	_	[213]
60 melanoma patients	_	_	_	High expression o HOTAIR was associated with a shorter OS rate.	_	_	[196]
30 melanoma patients	_	_	_	High expression of MHENCR was associated with a shorter OS rate.	_	_	[195]
64 EOC patients	_	_	_	High expression of MALAT1 was associated with a shorter OS rate.	_	_	[162]

Declaration of Competing Interest

The authors report no declarations of interest.

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